American Heart Journal

An international publication for the study of the circulation

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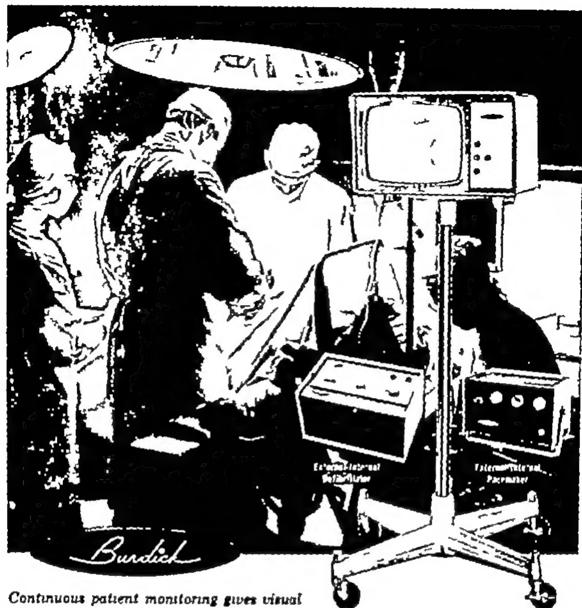
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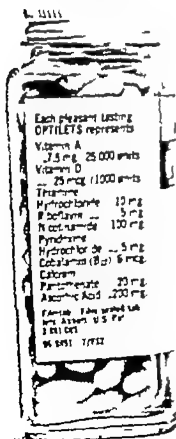
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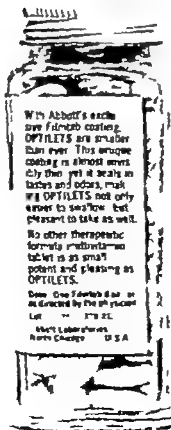
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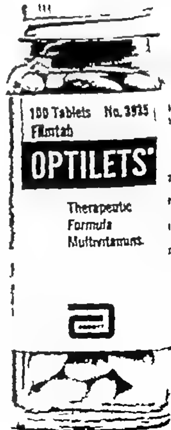
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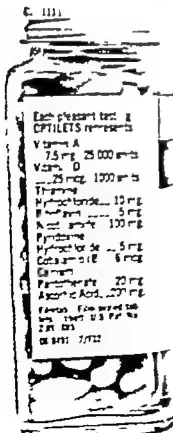
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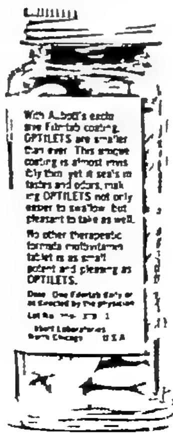
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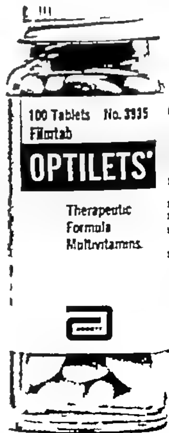
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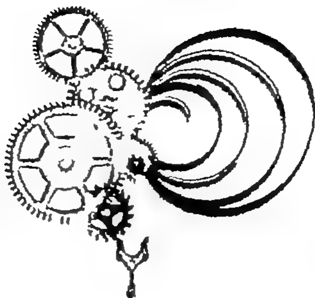
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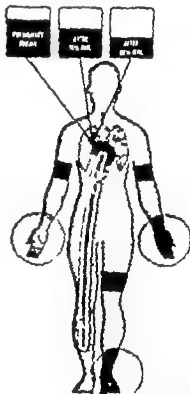






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American Heart Journal

July 1963 Volume 66 Number 1

Editorial

Pulmonary hypertension Individual and species variability relative to vascular reactivity

Robert F Grover M.D Ph.D
John H K Vogel M.D
Keith H Averill M.D
S Gilbert Blount Jr M.D
Denver Colo

A given stimulus will often provoke a spectrum of responses which vary in magnitude from one individual to the next. Indeed biologic systems seem to be characterized by inherent differences in reactivity. A familiar example is the biologic assay of a drug to determine its LD_{50} all animals receive the same stimulus (dose) but only half react adversely (die)

It is remarkable how seldom this well known concept enters into discussions of the pulmonary circulation. In our understanding of systemic hypertension we recognize and appreciate a great variability of response. Yet in considering pulmonary hypertension only Wood[1] and Short[2] have used such terms as *hyperreactive* or *hyporeactive* to indicate underlying differences in pulmonary vascular reactivity between individuals.

That such variability does actually exist is apparent when one examines the response of the pulmonary vascular bed to such stimuli as elevation of pulmonary venous pressure, increased blood flow or hypoxia. Wood[1] has observed that among patients with critical mitral stenosis, only 25 to 30 per cent develop severe pulmonary hypertension. Why does this group have a marked increase in precapillary vascular resistance whereas another 30 per cent with equal elevation of left atrial and pulmonary venous pressures have virtually no such vascular reaction?

In congenital absence of one pulmonary artery the flow of blood through the other pulmonary artery is twice normal from birth. A recent review disclosed that, when this was the only cardiovascular abnormality 19 per cent of such patients had severe pulmonary hypertension

A similar situation results from a congenital cerebral arteriovenous fistula. When such a fistula is large, cardiac output and pulmonary blood flow are abnormally increased from birth. Among infants in heart

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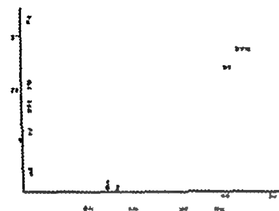


Fig. 1. M[illegible] rial pressure at rest [illegible] breathing [illegible] plotted [illegible] the large [illegible] pres[illegible] (From Vogel, et [illegible] Med [illegible] permission of the publisher [illegible] New York.)

f[illegible] use 25 per cent had severe [illegible] vascular changes.[9]

The pulmonary vascular bed is also subject [illegible] in blood flow when [illegible] shunt occurs through a [illegible] septal defect. This condition [illegible] those just mentioned in that [illegible] pulmonary circulation has relatively [illegible] with the high pressure sys[illegible] illustrations of this entity all [illegible] pulmonary arterial pressure are seen. It is often postulated that a direct relationship exists between the size of the defect and the elevation of the pulmonary arterial pressure. However, Lucas and associates recently analyzed a group of patients all of whom had large-sized defects, and found a wide range of pressures, a finding that we have also noted. Since the hemodynamic stress was similar in all these patients, they concluded that variation in pulmonary vascular reactivity between individuals must be responsible for the range of pressure produced.

What determines the pattern of response of the pulmonary vascular bed in a given individual with a ventricular septal defect? At present we do not know. However, it is of interest that many patients with small ventricular defects, normal pulmonary arterial pressures, and very little increase in pulmonary blood flow will exhibit a grossly exaggerated response of pulmonary arterial pressure to hypoxia. There is no apparent explanation for the hyperreactivity of these individuals.

Chronic hypoxia tends to bring out the latent differences among normal individuals in terms of pulmonary vascular reactivity. When 28 normal high school students who resided at 10,150 feet were studied by catheterization of the right side of the heart, about 20 per cent developed severe pulmonary hypertension during exercise or when breathing 13 per cent oxygen.[9] In contrast to these hyperreactors, another segment of this catheterized group had virtually no rise in pressure with 13 per cent oxygen and very little rise during exercise (Fig. 1).

Significant pulmonary hypertension is reflected in the electrocardiogram by the position of the mean QRS axis in the frontal plane. When Peñaloza and associates conducted an electrocardiographic survey of permanent residents at 14,900 feet altitude, they found a wide range in the QRS axis, which implied varying degrees of pulmonary hypertension; cardiac catheterization confirmed this. Examination of a comparable group of residents at sea level yielded a much narrower range in the QRS axis. No pulmonary hypertension was present. Thus, when a population of normal individuals is subjected to the stimulus of the chronic hypoxia of high altitude, the hyperreactors have the opportunity to distinguish themselves from the hyporeactors, and the entire gamut of pulmonary hypertension appears.

Variable degrees of pulmonary vascular reactivity are also seen in animals. When cattle were taken to an altitude of 10,000 feet, about one third developed severe pulmonary hypertension.[11] However, under the more severe hypoxic stress of 12,700 feet, all cattle became markedly hypertensive,[12] yet lambs at this same altitude retained normal pulmonary arterial pressures. The difference between species is also brought out when the stimulus is an increase in pulmonary blood flow from birth. Ligation of the left pulmonary artery routinely produces severe pulmonary hypertension in neonatal calves but never in newborn lambs.[13,14] As a species, cattle are hyperreactors, whereas sheep are hyporeactors. If we could discover the basis for this difference between species, we might have a clue to the variation in human pulmonary vascular reactivity.

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Clinical communications

Right atrial myxoma

Report of two cases and review of the literature

James F Morrissey M D
Frank L Campeti M D
Earle B Mahoney M.D
Paul N Yu M D
Rochester N Y

The availability of surgical techniques for the successful removal of myxomas of the heart makes an early and accurate preoperative diagnosis of great importance

In the past 3 years we have had the opportunity of studying 2 patients with right atrial myxoma We have also reviewed the 16 cases reported in the English literature in which the antemortem diagnosis of this lesion was made The purpose of this paper is to describe the clinical physiologic and angiocardiographic findings in these patients and to elucidate the diagnostic features and characteristics of this lesion

Case reports

Case 1 G W a 38-year-old white married woman was first seen in the Cardiopulmonary Laboratory in March 1959 with 3-year history of progressive dyspnea on exertion and easy fatigability During the previous year she had noted several episodes of transient lightheadedness, which generally occurred with exertion. On at least four occasions the patient experienced syncope without associated convulsive movements. There were occasional episodes of transient pain in the left lateral chest unrelated to exertion. She denied cough hemoptysis, orthopnea or peripheral edema. There was no history of fever diaphoresis or other hypermetabolic symptoms. During the previous year she had been given digitalis, without improvement in symptomatology Her past health had been excellent, and there was no history of rheumatic fever

On physical examination the patient was not in acute distress The blood pressure was 110/75 mm Hg the pulse was [illegible] and regular There was distention of jugular veins, with prominent "a" wave The lungs were clear The heart was enlarged 1 cm to the left of the mid-clavicular line in the fifth intercostal space. The rhythm was regular A Grade 2 rumbling diastolic murmur with presystolic accentuation was heard along the left sternal border and at the apex, unchanged with position. No systolic murmur or opening snap were audible. The pulmonic second sound was slightly accentuated The liver was palpable 6 cm. below the right costal margin. There was no peripheral edema

Laboratory studies revealed hematocrit of 42 per cent, white blood cell count of 8,000 with a normal differential and a corrected erythrocyte sedimentation rate of 35. Blood urea nitrogen and electrolytes were normal

Roentgenograms of the chest (Fig 1) demonstrated enlargement of the transverse diameter of the heart. Fluoroscopy confirmed cardiac enlargement, particularly of the right heart chambers, with vigorous pulsations at the apex and along the right cardiac border There was no evidence of deviation or compression of the esophagus with barium swallow

The electrocardiogram showed normal sinus rhythm with prominent P waves especially in Lead

From the Departments of Medicine Surgery and Radiology University of Rochester School of Medicine and Dentistry and the Medical and Surgical Clinics of the Strong Memorial and Rochester Municipal Hospitals, Rochester N Y
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Received for publication Aug 1 1961
Address, Strong Memorial Hospital, 260 Crittenden Blvd Rochester 20, N. Y

I II V, and V A QS complex was present in Leads V . The complexes were of low voltage throughout, and the T w es were flat.

The results of cardiac catheterization re outlined in Table I Cardiac output was less than one half normal nd failed to increase significantly during exercise. There was a persistent gradient between the right trium and ventricle which increased du ng exercise. There was giant 'a w ve in the right trial tracing (Fig 2).

Indicator-dilution curves which were recorded from the brachial artery after sequential injections of Cardiogreen into the chambers of the right side of the heart and pulmonary artery showed no evidence of left to-right intracardiac shu t However the dilution curve inscribed fter injection int the right trium was definitely broader and had disproportionately prolonged ascending and descending limb than those recorded when the indicator was injected distal to the tricuspid valve. These studies were thought to confirm the diagnosis of tricuspid stenosis and the slight elevation in pulmonary wedge pressure during exercise was thought to be compatible with associated mild mitral stenosis.

Exploratory cardiotomy was performed in June 1959 Examination of the left heart revealed no abnormalities. The right trium was large and tense nd was found to contain mass that partially filled the right trial ca ity It was thought that the patient had a right trial myxoma and that this lesion was amenable to removal by open cardiotomy using the pump oxygenator therefore, no further manipulation was ttempted.

Subsequently cineangiocardiographic tudies were performed. The right heart cavities, especially the trium were enlarged. A large polymorphic filling defect of the right trium and ventricle was demon strated, nd this was thought to be consistent with tumor of the right atrium implanted on the superior triocaval junction (Fig 3). This tumor passed through the tricuspid valve nd involved the inflow chamber of the right ventricle, as well as the inferior portion of the inf ndibulum

I July 1959 excision of the myxoma was t tempted. At triotomy the pedicle of the tumor was seen to originate from the margin of the trium just below the superior vena cava Although there was

Table I Catheterization data on Patient G W

	Rest	*Exercise*
Cardiac output (L./min.)	3 78	4 59
Pressures (mm Hg)		
Right trial		
	12	25
Mean	10	14
Right ventricular (systolic/diastolic)	28/2	26/3
Pulmonary arterial (systolic/diastolic)	27 '6	26/10
Pulmonary wedge	4	13



Fig 1 Posteros terior chest film showing cardiac enlargement with prominence of right heart border nd normal pulmonary asculature in Patient G W

some fragmentation during removal of the tumor no residual tissue was noted in the right trium t the time of losure of the triotomy The patient toler ted the procedure well, but cardiac arrest suddenly occurred as she was being removed from the oper ting table. At postmortem rather large portion of the tumor was found free in the right trium occluding the orifice of the tricuspid valve. It was believed that this represented portion of the tumor which extended into the inferior ena cava, was fragmented and held in place by the occlusive tape around the inferior caval catheter nd which was than able to float free t the conclusion of the oper tive procedure. The tumor displayed the charac teristic histologic features ascribed to myxomas of the heart.

COMMENT This case illustrates several important diagnostic features of right trial myxoma. The patient presented with history of syncope and progressive dyspnea (without orthopnea) which was refractory to digitalis and diuretic therapy On physical examination she had prominent wave in the jugular enous pulse and presystolic murmur long the lower left sternal border nd pex. Because w did not consider the possibility of myxoma, ere misled into believing that she had tricuspid stenosis and mild mitral stenosis.

Case 2 E.H. 47 year-old white married woman, was first seen in December 1959 She had been i good health until approximately 3 years previously when she noted the onset of easy fatigability which progressed in severity nd remained as her major complaint throughout the course of her illness. Approximately 2 years previously she was found t be nemic Treatment with iron did not relie her symptoms. Eighteen months prior to her isit to this hospital heart murmur as noted nd she sub-equently developed intermittent edema of both nkles. Because of increasing peripheral edema nd

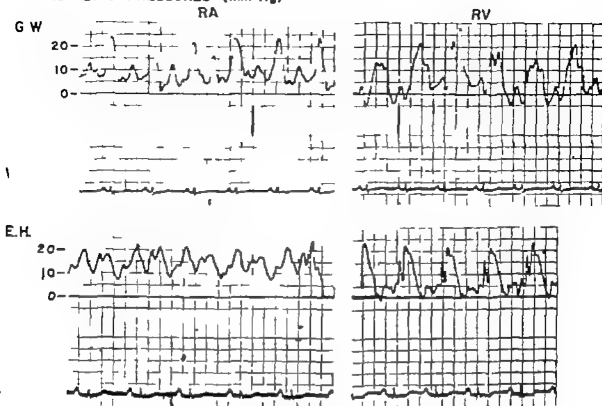


Fig 2 Right atrial (*RA*) nd right entricular (*RV*) pressure tracings and electrocardiograms recorded from the 2 patients G W nd E. H Not eles ted right trial pressure w th prominent wa e and persistent diastolic pressure gradient from the right trium to the right entricle in each case.

abdominal girth, she w hospitalized elsewhere in August 1958. Pertinent findings were a normal blood pressure peripheral pulses of decreased intensity

Grade 2 ystolic m rmur over the base of the heart nd left ternal border 4-fingerbreadth hepatomegaly and pitting edema t the knees. The hema tocrit wa 35 per cent, and the corrected sed menta tion rat was lev ted to 40 mm. per hour She was intermittently febrile with temperatures to 102°F During hospitalization to-and-fro sound became audible over the lower sternum this aried i ntensity nd was thought t be suggestive of pericarditis. Electrocardiograms showed low oltage Subacut bacterial endocarditis was suspected, but serial blood cultures were negative She improved lightly on digitalis nd diuretic therapy nd her discharge diagnosis wa activ rheumatic heart disease She was maintained on salt estriction nd digitalis, but ea y fatigability low-grade fever nd recurrent ankle edema continued. At no time did she experience significant dy pnea, nd there was no orthopne paroxysmal nocturnal dyspnea yncope ertigo, cough hemopty i or pain in the chest. There was no history of rheumatic fever

Physical examination t the time f her i itial isit to this hospital howed blo d pressure of 125/85 mm. Hg nd a pulse rat of 84 She w neither cyanotic nor dyspneic There wa mild d tention of the jugular eins, with prominent a w ve pulsations. The chest was clea to percussion and auscultation. The heart was not enlarged t percussion, nd the rhythm was regular A loud grating friction rub was heard most clearly t the left sternal border in the fourth i tercostal space nd toward the pex of the heart, synchronous ith the heartbeat and softer i diastole There was sepa rate systolic murmu long the left sternal border The second pulmonic sound w mildly accentuated nd a protodiastolic heart sound w heard t the pex nd long the left ternal border The first mitral sound was not accentuated, nd no opening snap wa heard. Slight peripheral edema w present.

Laboratory data revealed hematocrit of 35 per cent whit blood cell count of 9,000 with a normal differential, nd corrected sedimentation rat of 43 Urinalysis blood urea itrogen nd lectrolytes nd protei fractionation ere ll ithi normal limits.

Roentgenograms of the hest (Fig 4) showed some generalized cardiac enlargement with prominence of the right he rt cavities confirmed by fluoroscopy No deviation or impression f the esophagus w evident by barium llow

The lectrocardiogram howed normal sinus rhythm low ltage nd incomplet right bundle branch bl k. The P a es w re prominent in Leads II III nd V

The result of catheterization studies of the right side of the heart performed in February 1961 are outlined in Table II. There was slight arterial blood desaturation at rest. Cardiac output was low at rest. The resting systemic arterial, pulmonary arterial, pulmonary wedge and right ventricular pressures were normal. The mean right atrial pressure was elevated, with a diastolic gradient of 8 mm. Hg across the tricuspid valve. The right atrial and right ventricular pressure tracings are shown in Fig. 2.

Indicator-dilution curves were recorded after injections of Cardiogreen were made into the right side of the heart and pulmonary artery (Fig. 5). *The findings were similar to those in Case 1.*

Obstruction at the tricuspid valve was suspected and cineangiocardiographic studies were performed after the injection of radiopaque medium into the superior vena cava. A rounded nonopaque mass was found to occupy the right ventricle up to the outflow tract (Fig. 6). In continuous projection this large





Fig. 3. Two selective frames of the cineangiocardiogram and their respective diagrams obtained in Patient G. W. demonstrating the position of the myxoma as evidenced by the silhouette of the filling defects. Frame *A* was obtained at the end of ventricular diastole, whereas frame *B* was obtained at the end of ventricular systole.

filling defect moved to and fro through the tricuspid valve. These findings were thought to be consistent with pedunculated myxoma.



Fig. 4 Posteroanterior chest film showing some generalized cardiac enlargement with prominence of the pulmonary artery trunk, and fairly normal pulmonary vessels in Patient E. H.

Open cardiotomy with cardiopulmonary bypass and hypothermia was performed in April 1961. When the right atrium was opened the tumor presented as a reddish-gray gelatinous mass, 10 cm. in diameter, partially prolapsing through the tricuspid valve. When this was delivered it was attached to the atrial septum at about the foramen ovale by a narrow stalk 1.5 cm. in diameter. It was possible to deliver the mass completely with its capsule intact. The patient tolerated the procedure well and her postoperative course was uneventful. Pathologic studies confirmed the diagnosis of atrial myxoma.

Convalescence has proceeded satisfactorily and at the time of the present writing the patient has no cardiorespiratory symptoms. A Grade 2 systolic murmur along the left sternal border thought to represent tricuspid insufficiency was present post

Table II Catheterization data on Patient E.H

Arterial oxygen saturation (%)	90 52
Cardiac output (L./min.)	3 78
Pressures (mm. Hg)	
Right atrial	
"a" wave	14
Mean	10
Right ventricular (systolic/diastolic)	20/2
Pulmonary arterial (systolic/diastolic)	20/10
Pulmonary wedge	5

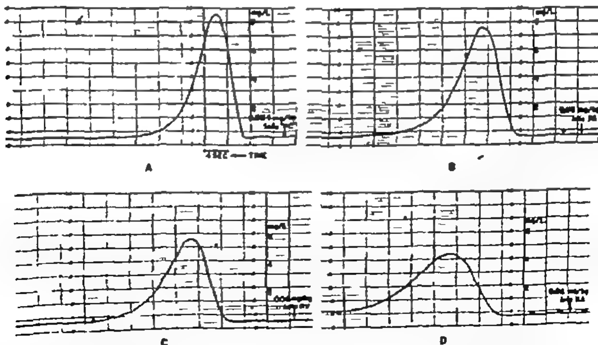


Fig. 5 Indicator-dilution curves inscribed by sampling blood from a systemic artery after injection of indocyanine green into the pulmonary wedge position (A), main pulmonary artery (B), right ventricular (C), and right atrium (D). Note that the curve inscribed after right atrial injection has a broad base and disproportionately prolonged ascending and descending limbs. These changes in the contour of the dilution curve are consistent with incompetency of the tricuspid valve.

operatively but was not while at the time of our last examination in September 1961.

Postoperative catheterization studies were performed in September 1961. There had been marked improvement in her cardiac status since operation with normal arterial oxygen saturation (98 per cent), increase in cardiac output to 6.2 liters per minute and no evidence of obstruction to flow in the right heart. Indicator-dilution curves entirely normal after injection of Cardiogreen into the right atrium with sampling of blood from brachial artery.

COMMENTS. Easy fatigability, low-grade fever, anemia, persistently elevated sedimentation rate, and loud friction rub along the left sternal border were prominent features of this patient's illness. When a gradient across the tricuspid valve demonstrated at catheterization, right atrial myxoma was suspected, on the basis of our experience in Case 1. The diagnosis was confirmed by angiocardiography.

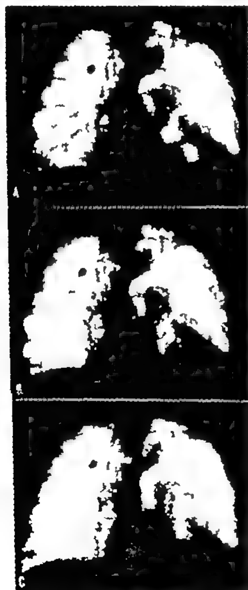




Fig. 4. Three selected frames of the cineangiocardiogram and their respective diagrams obtained. Patient E. H. At the end of ventricular diastole (frame *A*) the myxoma, as shown by the filling defect, occupies the right ventricular cavity and atrioventricular canal. During ventricular systole (frames *B* and *C*) the tumor is forced back into the right atrium.

Table III

Case	*Sex Age*	*Clinical features*	*Physical finding*	*ECG*
1 Bab son nd Newman	F 54	Dyspnea generalized edema ref actory t therapy	Distended cervical veins edema scites. Systolic and dia tolic murmurs t LSB	
2. Laquet et l	M 39	Right heart failure inter mittent cyanosis and dy pnea	Cervical vein d stention N cardiac murmu	RBBB peaked P w ves
3 Buenger et l	M 16	Ea y fatigability dyspnea	Cervical vein distention Systolic nd diastolic murmurs at LSB	RBBB broad P wa es I A V block
4 C ates and Dr k	F 50	Dyspnea easy f tigability fever nd light eat	Apical and pulmonic sys tolic murmurs ariable third heart sound	Sinu tachycardia low voltage QS I V
Lynns et l	M 51	Right heart failure syncope	Cervic l vein distention Loud pres ystolic murmur over tricuspid rea	QS I V s in giant I w ves in II III pre cordial lead
6 F B et l	M 48	Mild dyspnea generalized edema	Cervical ein distention ascites. f iction rul nd systolic murmur t LSB	Atrial fibr llation
7 Kra ll et l	F 14	Dyspnea weakness edema	Cervical ei distention. Systolic mu mur t tricuspid rea	RBBB
8 Cooley et l	F 43	Dyspnea	Cervical vei distention. No ardia murm ur	RAD low volt ge
9 Cooley et l	F 48	Dyspnea weakness edema	Cervical ei distention edema sites no cardiac m rmu r	Peaked P waves low oltage
10 Belle	F 43	Weakness generalized edema	Presy tolic murmur t LSB	Low oltage promi nent I wa es
11 Ladh m et l	M 46	Dy pnea weakness low grade fever intermittent diarrhea	Cervical vein distention Sy tolic nd diastolic mu murs at tricu pid area	Diff se T w v hanges
12 C mpea nd David	M 47	Mild dyspnea edema nd ascites	Ascites systolic and dias tolic murmurs t LSB	RBBB Low ltage
13 A hma et L	M 38	Dyspnea syncope recu rent w kness	Presy tolic murmu at LSB	Peak P w ves in V low ltage
14 Taber et l	F 51	Dy pnea night weat	Neck ei d stention Sys t lic murmur over tricus pid rea nd i termittent diastolic murmur at LSB nd pex	Low oltage
15 T ber et l	F 54	Dy pnea palpitations	Cervical ei distention edema. Systolic nd dias tolic murmurs t LSB	Peaked P waves
16. Adams et L	M 31	Dyspnea weakness syncope	Cervic l ei distention Dia tolic murmu and third heart sound at LSB	RBBB Large I w es
17 Morrissey et l	F 38	Dyspnea fatigability syncope	Cervical ein distention. Diastolic murmur t LSB nd pex	QS in V low olt age peaked P es
18. Morrissey et L	F 47	F tig bil ty edema low grade fever	Cervical ein distention Sy t lic murm friction rub t LSB	RBBB prominent I w es low oltage

LSB Lef sternal border RBBB Right bundle branch block RAD Right axis deviation C O Cardiac output T V Tricuspid l alv

Roentgenography	*Cardiac catheterization*	*Surgery*	*Results*
Normal	Low C.O., elevated RA pressure	Exploratory cardiotomy	Postoperative death due to residual tumor
Right heart enlargement	Diastolic gradient of 5 mm. Hg across T.V.	Tumor removed at exploratory cardiotomy	Postoperative death
Right heart enlargement; mobile calcified mass observed in RA at fluoroscopy	Elevated RA pressure	Removal attempted during exploratory cardiotomy	Operative death due to multiple pulmonary emboli
Right heart enlargement	Right-to-left shunt at atrial level	Cardiopulmonary bypass	Recovery, asymptomatic
Generalized cardiac enlargement	Diastolic pressure gradient of 25 mm. Hg across T.V.	Cardiopulmonary bypass	Postoperative death due to massive T.I.
Cardiomegaly primarily in RA	Diastolic gradient of 8 mm. Hg across T.V.	Cardiopulmonary bypass	Mild residual T.I.
Right heart enlargement; calcified mass in RA		Hypothermia	Mild residual T.I.
Right heart enlargement	Diastolic gradient of 7 mm. Hg across T.V.	Removal of myxoma attempted at exploratory cardiotomy	Operative death
Generalized cardiomegaly	Diastolic gradient of 15 mm. Hg across T.V.	Cardiopulmonary bypass	Recovery, asymptomatic
RA enlargement	Low C.O., diastolic gradient of 5 mm. Hg across T.V.	Hypothermia	Postoperative death
Normal	Diastolic gradient of 5 mm. Hg across T.V.	Hypothermia	Recovery, asymptomatic
Right heart enlargement	Diastolic gradient of 8 mm. Hg across T.V.	Cardiopulmonary bypass	Mild residual T.I.
Normal		Cardiopulmonary bypass	Recovery, asymptomatic
Normal	Right-to-left shunt at atrial level	Cardiopulmonary bypass	Recovery, asymptomatic
Normal	Diastolic gradient of 15 mm. Hg across T.V.	Cardiopulmonary bypass	Recovery, asymptomatic
Right heart enlargement	Diastolic gradient of 10 mm. Hg across T.V.	Cardiopulmonary bypass	Postoperative death in biventricular failure
Generalized cardiac enlargement, predominantly right heart	Low C.O., diastolic gradient of 8 mm. Hg across T.V.	Cardiopulmonary bypass	Postoperative death due to residual tumor
Mild generalized cardiomegaly predominantly right heart	Low C.O., diastolic gradient of 8 mm. Hg across T.V.	Cardiopulmonary bypass	Recovery, asymptomatic

T.I. Tricuspid incompetence.

Discussion

Table III summarizes the findings in the reported cases of right atrial myxoma.[1] On the basis of our experience with 2 patients with right atrial myxoma and a review of the literature it is important to comment on several characteristic features of this lesion

Clinical features Intracavitary myxomas have been found in patients over a wide age range but more commonly they occur in patients between the ages of 30 and 60 years.[4,16] In this series, over 70 per cent of the cases occurred in the fourth and fifth decades. Although the ratio of males to females with myxomas has been estimated as approximately 1 to 3[16] an equal sex incidence was noted in the present series 8 males to 10 females.

Right heart failure was evidenced in all patients in this series manifested by distention of cervical veins prominent a waves in the jugular venous pulse hepatomegaly ascites and peripheral edema These findings are readily explained on the basis of mechanical interference with atrial or ventricular filling or both Exertional dyspnea weakness, and easy fatigability are frequent symptoms, related undoubtedly to reduced cardiac output which has been demonstrated in several patients at cardiac catheterization The absence of orthopnea and paroxysmal nocturnal dyspnea is characteristic in none of these patients was there objective evidence of left heart failure A rapidly progressive course or periods of relatively good health interrupted by episodes of acute cardiorespiratory distress and lack of response to digitalis and diuretic therapy as evidenced by several patients in this series are prominent features of intracavitary tumor and may suggest the correct diagnosis for the first time A history of dizziness and syncope was recorded in 6 patients. In 2 the episodes were definitely related to a change in body position this is an excellent clue to the presence of an intracardiac tumor [17] Intermittent low grade fever and night sweats were prominent symptoms in 4 patients and suggested bacterial endocarditis. Blood cultures were uniformly negative however Although systemic emboli have been described in patients with left atrial myxoma and may dominate the clinical picture [14,15] objective evidence for pulmonary emboli is not apparent from this study

The most characteristic auscultatory finding in right atrial myxoma is a low pitched rumbling diastolic murmur along the lower left sternal border which may or may not change with respiration or position mimicking organic tricuspid stenosis. This finding was described in 11 of the 18 patients and in 7 instances was accompanied by a systolic murmur along the left sternal border consistent with tricuspid insufficiency Other auscultatory findings were an isolated systolic murmur along the left sternal border (3 patients) a diastolic third heart sound along the left sternal border (4 patients) and a friction rub along the left sternal border (2 patients) An opening snap was not described in any of these patients. In 3 patients no auscultatory abnormalities were described Perhaps the most important auscultatory clue in atrial myxoma is the variability of murmurs in the same patient on successive days or the disagreement among reliable observers in their auscultatory findings

Myxomas, especially of the left atrium *simulate the various manifestations of* rheumatic heart disease more than any other clinical entity Patients with myxomas however generally have a course of events unusually shortened in time for the usual patient with valvular heart disease [4] None of the patients in this series gave a history of rheumatic fever and the 2 patients whom we studied had no known heart murmurs prior to the onset of cardiac symptoms. Other diagnostic considerations in several patients in this series were constrictive pericarditis, nonspecific pericarditis, myocarditis, Ebstein's anomaly carcinoid tumor and superior vena caval obstruction In none was coronary heart disease suspected

In summary the clinical course of patients with right atrial myxoma is characterized by progressive unexplained obstruction to the lesser circulation without evidence of underlying pulmonary disease or left heart failure

Routine laboratory studies No consistent abnormalities are evident from routine laboratory studies in this investigation

Two patients were anemic, 2 had persistent leukocytosis, and 5 patients, including the 2 whom we studied, had persistently elevated sedimentation rates. These findings, in association with fever and elevation of gamma globulins in some patients, have raised the question of a systemic reaction to degenerative changes in the myxomatous tissue.

Electrocardiogram. Electrocardiographic changes, when present, are not specific. However, as can be seen from Table III, low voltage and prominent P waves, especially in Leads II, III, and V_{1-2}, are frequent findings. Right bundle branch block and QS pattern in Leads V_{1-2} are less frequent findings. It is pertinent that in this series all the patients except one had normal sinus rhythm, which is unlike the usual situation in progressive valvular or myocardial disease, wherein auricular fibrillation is a common feature.

Roentgenologic findings. Roentgenologic studies showed cardiac enlargement in 13 of these 18 patients. In most instances this represented right atrial and right ventricular enlargement, although generalized cardiac enlargement was not unusual. In 2 patients a calcified mass was observed within the right atrium at fluoroscopy. A uniform finding and valuable diagnostic sign in these patients was the absence of vascular engorgement in the lungs despite advanced evidence of right heart failure.

Cardiac catheterization findings. In an ill-defined case of heart disease, cardiac catheterization studies may contribute appreciably to the definitive diagnosis. All but 2 patients in this series on whom cardiac catheterization was performed had right atrial hypertension and a diastolic pressure gradient across the tricuspid valve which ranged from 5 to 16 mm. Hg. The 2 exceptions were patients with a variable right-to-left shunt at the atrial level. Uniformly normal pressures were observed in the right ventricle, pulmonary artery, and pulmonary wedge position. Because of a borderline elevation in the pulmonary wedge pressure during exercise in Case 1, we were misled into assuming that she had mild mitral stenosis in addition to tricuspid stenosis. Isolated tricuspid stenosis in the adult is such a rare lesion that angiocardiography should be performed in any patient in whom a gradient across the tricuspid valve is demonstrated during right heart catheterization. Bahnson and Newman[3] pointed out that the atrial pressure curve may show its lowest dip just prior to ventricular contraction, a feature against tricuspid stenosis and suggesting a ball valve mechanism between the atrium and ventricle. However, the right atrial pressure tracings in the 2 patients whom we studied were indistinguishable from those seen in proved tricuspid stenosis.

Indicator-dilution curves. There is no evidence of intracardiac shunt. The large area of the curves usually indicates a low cardiac output. In both of our patients the dilution curve inscribed after the indicator was injected into the right atrium showed a disproportionately prolonged ascent and descent, with a broader contour than those recorded when the indicator was injected distal to the tricuspid valve.

Angiocardiography. Angiocardiography is the most definitive tool in the diagnosis of right atrial myxoma, and it would seem wise to proceed directly with this study in patients who are suspected of having this lesion on the basis of the signs and symptoms discussed above. A characteristic filling defect was noted in all 12 patients in this series on whom this study was performed. In addition, this technique, in preparation for operation, allows some estimate of the size of the tumor, its location, and the site and type of attachment to the atrial wall. Although the presence of a large atrial thrombosis cannot always be differentiated by this study, a to-and-fro movement of the filling defect through the tricuspid valve in continuous projection favors the diagnosis of myxoma, as demonstrated in Case 2.

Surgery and course. In 10 of these 18 patients the tumor was successfully removed. Prior to the development of methods of open heart surgery the results of attempted surgical removal of atrial myxomas were poor. Four patients in this study died when removal of the tumor was attempted at exploratory cardiotomy. In 2 of 3 patients, successful excision was performed utilizing hypothermia, but the limitations of this method, particularly the high incidence of arrhythmias, favors the use of cardiopulmonary bypass with

a pump oxygenator. This method provides optimum conditions of exposure and operating time to permit total excision of this lesion and careful removal of any loose fragment of tumor to prevent embolism. In of 10 patients the tumor was successfully removed utilizing this technique and it is likely that with further experience the mortality rate will be reduced. Massive tricuspid insufficiency occurred postoperatively in 1 patient and may on occasion compromise an otherwise successful operation. Four patients were thought to have mild residual tricuspid insufficiency after operation. The patient whom we have followed had a systolic murmur along the left sternal border and some prominence of the v waves in the jugular venous pulse for several months postoperatively but these findings had disappeared at the time of our last examination. The 10 patients in whom the operation was successful realized a striking relief of symptoms. This was confirmed hemodynamically by postoperative cardiac catheterization in our patient.

Summary

Two cases of right atrial myxoma are presented together with a review of 16 other published cases.

The clinical course of these patients is characterized by progressive right heart failure usually refractory to medical therapy without evidence of underlying pulmonary disease or left heart failure. A low pitched diastolic murmur along the lower left sternal border is the most characteristic auscultatory finding.

Right atrial hypertension and a diastolic gradient across the tricuspid valve are consistent findings at cardiac catheterization.

Angiocardiography is the definitive diagnostic method for establishing the diagnosis of right atrial myxoma and a characteristic filling defect is noted in every reported case.

Since cure may be obtained by utilizing open heart surgery with cardiopulmonary bypass, an early and accurate preoperative diagnosis is of great importance.

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Mitral stenosis in childhood: Clinical and therapeutic aspects

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Descriptions in the literature of mitral stenosis and of its surgical therapy in childhood are scanty. This is due to the relatively rare incidence of rheumatic fever in persons under 6 years of age and to the fact that there is usually a lapse of 2 to 3 years and often longer between the onset of endocarditis and the development of mitral stenosis.[11,22,28] Moreover, the fear of recurring rheumatic fever in young subjects who have a recent history of their first episode has often advised limiting operative indications in this group of patients.

Thus, the largest series reported to date are those of Borman and associates[4] with 13 patients, 9 to 16 years old; of Brest and associates, who report on 15 patients, 16 to 20 years old; of Soulié and associates[3] with 12 patients ranging from 9 to 15 years of age; of Gibert-Queraltó and associates[13] with 24 patients 8 to 18 years old; and of Castle and Baylin with 7 children. Bailey and Bolton,[3] in a series of 1,000 commissurotomies, have observed only 13 patients with mitral stenosis who were under 20 years of age; one case was that of a 4½-year-old baby. Angelino and associates[1] report on 11 patients who were between 8 and 16 years old in a series of 600 operated cases. Glover[13] reports fewer than 12 patients under 18 out of 1,500 cases. Other authors have reported isolated cases: Stuckey,[29] 1 case; Lurie and Shumacker[24] and Gray,[15] 3 cases each; Bradlow and Crawshaw, 4 cases. The rarity of these observations has encouraged us to report our statistics.

Material

The present study concerns 54 patients, 17 males and 37 females, ranging in age from 8 to 15 years, who were admitted to the Institute of Surgical Pathology from 1950 to 1958 and the Surgical Clinic of the University of Rome from 1959 until the present date. Of these, 48 were subjected to mitral commissurotomy (15 males and 33 females) out of a series of approximately 2,000 patients operated on in the same period. The characteristics of the group under discussion are summarized in Table I.

The average age of the entire group was 13 years, whereas that of those who were operated on was 12.7 years. Catheterization of the right side of the heart was performed in 26 patients; one patient under

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Table I

Age (yr.)	Number of cases	Cardiac catheterization		Diagnosis		
		Preoperative	Postoperative	Operative	Autopsy	Clinical
8	3— 1 Male Females	3	1	2	1	—
9	— —	—	—	—	—	—
10	1 1 Female	—	—	—	1	—
11	— 1 Male 6 Females	4	1	6	—	1
12	9— 4 Males 5 Females	5	4	9	—	—
13	13— 3 Males 10 Females	5	—	12	—	1
14	6— 3 Males 3 Females	3	—	5	1	—
15	15— 5 Males 10 Females	6	3	14	1	—
Total	54— 17 Males 37 Females	27	9	48—15 Males 33 Females	4	2

ent combined catheterization using the ansthoracic posterior approach to the ft atrium. Nine patients operated on were subjected to postoperative catheterization approximately 1 month after operation. In 4 of 6 patients not subjected to operation the diagnosis was confirmed at autopsy; in the other 2, operation was postponed because of the presence in one of marked rheumatic activity, and in the other of practically normal cardiopulmonary hemodynamics.

History. In 21 patients (39 per cent) there was a history of typical acute rheumatic fever with repeated episodes reported in. Eleven patients (20 per cent) had suffered from recurrent tonsillitis and 2 (4 per cent) from chorea. In 20 individuals (3 per cent) there was no clear history of rheumatic infection (Table II). The average age at the time of onset of the first bout of rheumatic fever was 8 years (from 5 to 14 years) and the average age at the onset of cardiovascular symptoms was 10 years, with an average interval of 2 years between onset of disease and the appearance of symptoms (minimum 6 months, maximum 10 years).

Symptomatology. In practically all patients there was an evident subjective symptomatology, oftentimes grave: exertional dyspnea was present in 98 per cent, dyspnea at rest and orthopnea in 32 and 35 per cent, respectively, acute pulmonary edema in 18 per cent, hemoptysis in 19 per cent, and peripheral edema in 10 per cent. Examining these findings in relationship to the age of the patients at the onset of symptoms, one finds that the most salient feature was the higher incidence of acute pulmonary edema in the younger patients of this series, that is, in those 11 and 12 years of age, whereas the appearance of peripheral edema and hemoptysis was more often seen in the older patients.

Table II

	Number of cases	Per cent
Acute rheumatic fever	21	39
Angina	11	20
Chorea	2	4
No history of rheumatic fever	20	37

ue in those 14 and 15 years of age. The erythrocyte sedimentation rate was often elevated being above the upper limits of normal in 58 per cent of the total group. All patients were classified in Class III or IV functional capacity according to the New York Heart Association classification with the exception of one patient in whom the limitation corresponded to Class II.[22]

Cardiac auscultation All patients presented somewhat similar and typical auscultatory findings a reinforced pulmonic second sound which was often split an apical first sound characteristically snapping and an opening snap in a high percentage of cases a diastolic rumble with a presystolic crescendo at the apex, many times audible along both sternal borders. In 12 patients a systolic murmur of varying intensity was noted at the apex, radiating toward the axilla in 4 patients. In 2 of these a mildly insufficient valve was reported at the time of operation In 4 patients the systolic murmur was also heard at the center and at the base of the heart Phonocardiograms were not obtained routinely and no detailed study of such recording was therefore attempted as recommended by Castle and Bayfin, who emphasize the importance of the Q wave—first sound minus second sound—opening snap" time in evaluating the severity of mitral stenosis.

Radiologic findings Roentgenographic studies, consisting of anteroposterior left anterior oblique right anterior oblique and left lateral projections, with barium meal esophagram were performed in all patients. Enlargement of the cardiac chambers and of the pulmonary artery was arbitrarily graded from 1 plus to 4-plus. All cases were evaluated by the same examiner From these findings an over-all conclusion was made in regard to cardiac enlargement, and again the grading was from 1 plus to 4-plus. In 56.6 per cent the enlargement was graded as 2 plus, in 32 per cent as 3-plus and in the other 11 4 per cent as 1-plus. Fig 1 illustrates the radiographic modifications in the study group. In addition the longitudinal and transverse diameters were measured and the cardiothoracic index was determined When our findings were compared with the normal values for the same age group according to Cloetens the heart enlargement was evident the average diameters being always greater than those of patients of similar age who were without cardiac pathology The differences for the longitudinal and transverse diameters ranged from 0.7 to 2.4 cm The cardiothoracic ratio in particular was altered in practically all cases, with an average value of 0.53 (from 0 45 to 0 64) We were not able to demonstrate any significant relationship between the degree of cardiomegaly and the age of the patient or the duration of symptoms in each case. In fact many times a 1 plus enlargement was seen in older patients who had had symptoms for several years, whereas a 2 plus or 3-plus enlargement could be observed at any age, with a duration of symptoms at times of only a few months.

Electrocardiogram In each instance an ECG was obtained using the standard limb leads, augmented unipolar limb leads, and precordial leads from V_{3R} to V_7 There was normal sinus rhythm in all patients, with evidence of left atrial hypertrophy pattern in 38 (70 per cent) In 34 patients (63 per cent) there was evidence of right ventricular hypertrophy none had left ventricular hypertrophy In 8 patients the ECG was not available for examination,

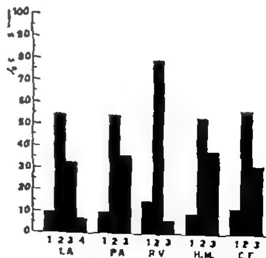


Fig 1 Radiologic findings graded 1-plus to 4-plus. LA. Left atrium. PA Pulmonary artery RV Right ventricle. H.M Hilar markings. C.E. Over-all cardiac enlargement. 1+ Questionable to slight enlargement. 2+ Slight enlargement 3+ Moderate enlargement. 4+ Marked enlargement.

Table III

		N Cases	Percent
Normal ECG		10	22
Left atrial hypertrophy isolated		7	15
Right vent. hypertrophy		2	4
Combined atrial & vent. hypertrophy		27	59
P wave morphology	I	16	35
	II	7	15
	III	6	13
	IV	5	11

and the only information was a written report made at the time of admission. In the other 46 patients the tracings were analyzed in detail and the following findings were noted.

Atrial tracings. The morphology, amplitude, and duration of the P wave, together with the P-R interval in Lead II were determined, and the P wave duration to P-R segment ratio was calculated according to Macruz.[7,8] The P wave morphology was found to be modified in respect to the normal configuration in 34 patients (74 per cent); it presented a notched descending limb in 35 per cent and a notched ascending limb in 15 per cent. Thirteen per cent of the patients were found to have an asymmetrical wave with a rapid upward stroke and a slow descending limb. The other 11 per cent possessed a tall, peaked P wave (Table III). The amplitude of the P wave varied from 1 to 5 mm., with an average height of 2.6 mm. In 12 patients (26 per cent) the P wave exceeded the maximal normal value of 2.5 to 3.0 mm. given for children. In 18 patients (39 per cent) the amplitude was at the upper limit of normal, whereas in the other 16 (35 per cent) it was within normal limits; however, the P wave configuration was often abnormal. The duration of the P wave ranged between 0.01 and 0.16 second, and in 16 patients (35 per cent) it was equal to or greater than the maximal normal value of 0.10 second.

The index of Macruz averaged 1.9 (from 0.8 to 4.0) and in 25 cases (54 per cent) it was higher than the maximal limit of 1.6 reported for normal electrocardiograms.[7,8,21] On the basis of these criteria there was evidence of left atrial hypertrophy in 34 patients (74 per cent), isolated in 7 patients (15 per cent) and combined with right ventricular hypertrophy in 27 (59 per cent) (Table III).

VENTRICULAR TRACINGS. The following measurements were noted: the amplitude of the R wave and the ventricular activation time (VAT) in Lead V_1 and the R/S ratio in Leads V_1 and V_6, the sum of the R wave in Lead V_1 and the S wave in Lead V_5, the R/S ratio in Lead V_6 divided by the R/S ratio in Lead V_1, and finally the Q/R ratio in Lead aV_R.[9,11,17,21,27] In 27 patients (59 per cent) the amplitude of the R wave exceeded the maximal normal value of 7.0 mm., and in some instances attained extremely high voltage of up to 25 mm. The ventricular activation time in Lead V_1 varied from 0.01 to 0.06

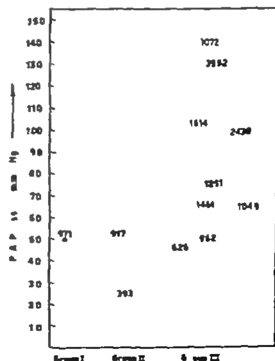


Fig. Relationship between pulmonary arterial pressure (dots) and pulmonary resistance (numbers), and electrocardiographic findings. Group I: Patients with normal ECG. Group II: Patients with isolated left atrial strain. Group III: Patients with right ventricular hypertrophy.

second with an average of 0.032 second and was greater than the maximal normal value of 0.03 second in 22 cases (48 per cent). The sum of the R wave in Lead V plus the S wave in Lead V was abnormally elevated in 13 per cent of the cases, with values up to 45 mm. (maximal normal value of 10.5 mm.). The R/S ratio in Lead V (maximal normal value of 1.0) was elevated in 62 per cent of the cases. The R/S ratio in Lead V divided by the R/S ratio in Lead V_1 (minimal normal value of 0.4) ranged between 0.01 and 40.0 and in 30 per cent of the cases it was indicative of right ventricular hypertrophy. Finally the Q/R ratio in Lead aV (maximal normal value of 1) presented evidence of right ventricular hypertrophy in 23 per cent of the tracings examined.

Thus if the indices—sum of the R wave in Lead V and S wave in Lead V and R/S ratio in Lead V—are retained as yielding the highest incidence of right ventricular hypertrophy, the latter was present in 63 per cent of the group studied. In only 2 patients was this hypertrophy isolated without alterations of the atrial tracing (Table III).

In 10 patients (22 per cent) the ECG was within normal limits in respect to both the atrial and ventricular tracings. Only 4 of these 10 patients were catheterized and their pulmonary arterial pressures ranged between 25 and 50 mm. Hg systolic. Valvotomy was performed on all except the patient with normal pulmonary pressure.

In those patients who had undergone cardiac catheterization the electrocardiographic signs of right ventricular hypertrophy were compared with the pulmonary arterial pressure and total pulmonary resistance. *A certain degree of correlation* was noted in that in those patients with electrocardiographic evidence of right ventricular hypertrophy the pulmonary arterial pressure was equal to or higher than 50 mm. Hg systolic. In the group with normal ECG or isolated left atrial hypertrophy there were no instances of marked pulmonary hypertension nevertheless the pressure exceeded normal values with the exception of one case (Fig. 2).

Hemodynamic findings. Cardiac catheterization was performed in 27 patients and repeated approximately 1 month after operation in 9 of these. The hemodynamic data are reported in Tables IV and V. In all but 3 patients the pulmonary arterial systolic pressure was 50 mm. Hg or higher with marked hypertension (above 80 mm. Hg) in 10 patients. Total pulmonary resistance calculated in 14 patients was high and above 1,000 dynes sec. cm.$^{-5}$ in 6 of these patients, and above 2,000 in 2. The pulmonary venous capillary or pulmonary arterial wedge pressure obtained in 19 patients, was rather markedly *elevated in most cases. Consequently the* pulmonary artery–venous capillary pressure gradient was relatively low and the pulmonary arteriolar resistance was comparatively less altered than the total resistance. Patient S.F. (Table IV) is the only one of the series with normal pulmonary arterial and venous capillary pressures and for this reason she was not operated on. Cardiac output ranged between 2.5 and 7.1 liters per minute with an average of 3.6 L. per minute, and was thus within the normal values for this age group.[28]

There was no evident relationship in this group between the degree of hemo*dynamic disturbance and the age of the* patients or the time elapsed since the first rheumatic episode or the first symptoms. In each catheterized patient the stenosis was tight with a valvular orifice that measured 1 cm. or less in diameter.

The last 4 patients listed in Table IV died during hospitalization before operation. In 3 patients (B.A., R.R., Di M.M.) death was caused by acute pulmonary edema which appeared in Patients B.A. and R.R. a few hours after cardiac catheterization. Patient P.A. after an episode of bronchopneumonia developed congestive heart failure which terminated in acute pulmonary edema. All 4 patients had a high degree of pulmonary hypertension associated with clinical and hemodynamic signs of failure: elevated right ventricular end-diastolic pressure and right atrial pressure. Autopsy revealed a markedly stenotic valve in all these cases.

Of the other 50 patients operation was withheld from one because of acute carditis and from another because of normal right heart catheterization data. Thus mitral valvotomy was performed in 48 patients.

Surgical findings and results. The mitral valve was found to be fibrotic in all patients. The diameter of the orifice was equal to or less than 0.5 cm. in 36 patients, from 0.5 to 1.0 cm. in 10, and approximately 1.5 cm. in the other 2, as estimated by digital exploration. In 7 patients the stenosis was complicated by a fusion of the chordae tendineae. A digital commissurotomy was performed in 44 patients, whereas in 4 others the application of an instrumental dilator was necessary, with

Table IX

Patient	Age (yr.)	Pressure (mm. Hg)				Resistance (dynes sec. cm.⁻⁵)		Cardiac output (L./min.)
		P.V.C.	P.A.	R.V.	R.A.	T.P.R.	A.P.R.	
A.L.	12	28	100/50	100/2	4/0	1 614	1 049	4
C.L.	13	25	100/40	100/8	8	—	—	—
de F.F.	13	—	42/12	—	—	—	—	—
d. C.L.	15	40	105/40	105/2	8/0	—	—	—
d. L.C.	15	12	50/20	50/0	10/0	—	—	—
D.C.	15	22	60/38	60/2	2	—	—	—
F.C.	8	50	98/80	98/10	9/4	2 430	926	2.8
L.S.	13	25	50/20	50/0	—	—	—	—
M.E.	14	—	60/35	60/5	6/2	—	—	—
P.G.	13		65/35	65/7	3/3	1 461	—	2.5
S.C.	13	—	85/40	85/0	6/0	—	—	—
S.P.	14	—	70/42	70/10	—	—	—	—
T.S.	11	40	78/50	70/0	4/0	—	—	—
S.F.	11	8	25/15	25/0	5/0	393	218	3.7
B.V.	8	50	140/78	140/10	8/2	—	—	—
di M.M.	10	25	75/45	75/15	16/10	1 251	746	4
P.V.	14	50	130/65	130/10	10/5	3 552	2 022	1.8
R.R.	15	38	115/65	115/8	8/2	—	—	—

P.V.C. Pulmonary venous capillary. P.A. Pulmonary artery. R.V. Right ventricle. R.A. Right atrium. T.P.R. Total pulmonary resistance. A.P.R. Arteriolar pulmonary resistance.

Table X

Patient	Age (yr.)	Pressure			
		P.V.C.		P.A.	
		Preop	Postop	Preop	Postop
C.M.	15	18	—	50/30	50/25
di L.A.	11	25	9	50/25	27/10
di M.R.	12		—	55/30	18/10
D'O. B.	12	29	28	90/50	68/22
F.L.	15	20	12	50/30	41/20
M.M.	12	30	8	65/35	15/10
R.V.	8		8	42/18	22/8
S.D.	15		12	140/75	45/18
S.L.	12	26	20	50/25	50/15

P.V.C. Pulmonary venous capillary. P.A. Pulmonary artery. R.V. Right ventricle. R.A. Right atrium. T.P.R. Total pulmonary

approach to the valve through the left atrial appendage. A satisfactory splitting was reported by the operating surgeon in 46 patients, with divulsion of both commissures in 27 patients, whereas in 2 patients the opening was considered to be inadequate. In 2 patients a mild regurgitant flow was noted prior to the attempt at commissurotomy in one of these patients the regurgitation disappeared after the valve was mobilized whereas in the other it was somewhat augmented. In 4 patients the surgical dilatation was followed by a slight to moderate degree of mitral insufficiency in 3 of these the stenosis was complicated by fusion of the chordae tendineae.

RESULTS The operative mortality was zero. The postoperative recovery was relatively uneventful However 4 patients presented in the third to fourth postoperative weeks a symptomatology suggestive of the postcommissurotomy syndrome. Three patients became clinically decompensated and one who appeared to be refractory to medical therapy finally died on the thirty fifth postoperative day One patient developed atrial fibrillation on the fifth day and it was not possible to convert this to normal sinus rhythm using digitalis and quinidine. The general and local cardiac conditions were considered to be quite satisfactory in the other 40 patients (83 per cent) at the time of their discharge from the hospital

Repeat cardiac catheterization was performed in 9 patients 20 to 30 days after operation The hemodynamic results are illustrated in Table V The systolic pressure in the pulmonary artery decreased in 7 of these patients, at times markedly so (Patient S D) in another 4 patients a return of the pulmonary arterial pressure to within normal limits was noted (Patients D M R. M M R.A and D L.A) In 2 patients, only the mean pulmonary arterial pressure was reduced whereas the systolic pressure was unchanged (Patients C M and S.L.) The total pulmonary resistance was diminished in all but one patient in whom the values remained unchanged (C M) The cardiac output was increased in all but 2 patients (D L.A and S D)

Of the 48 patients who underwent operation we were able to obtain late information about 38 in regard to their rehabilitation from periods of 1 to 8 years with an average follow-up period of 4 years. Of these 4 had died one after 1 year and another after 2 years with chronic congestive failure, another after 5 years, cause of death undetermined and the fourth after 5½ years due to the complications of chronic glomerulonephritis. These 4 patients plus the one previously mentioned

(mm. Hg)				Resistance (dynes sec. cm⁻⁵)				Cardiac output (L/min.)	
R.V		R.A		T.P.R.		A.P.R.			
Preop	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
50/10	55/8	10/5	8/2	626	626	320	—	4 5	5 1
50/0	33/0	2/0	4/0	917	726	371	363	3 7	2
—	—	—	—	—	—	—	—	—	—
90/5	68/3	4/2	10/3	1,565	752	888	262	3 4	4 6
50/5	44/8	5/0	10/2	962	645	396	403	2 8	4
68/7	15/0	7/0	2/0	1,049	182	444	61	4	5 2
42/2	22/3	—	6/0	824	358	—	133	2 9	3 1
140/8	45/5	7/0	5/0	1,072	464	—	278	7 1	5 2
55/0	50/10	2/0	7/1	971	361	248	225	2 9	7 1

resistance. A.P.R. Arteriolar pulmonary resistance.

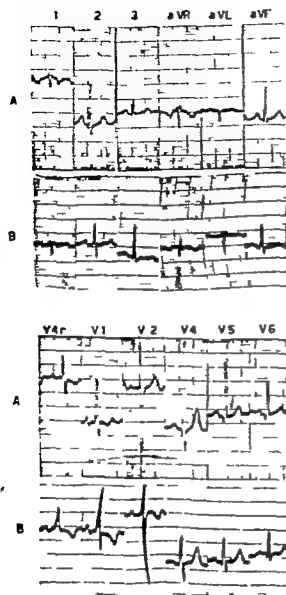


Fig 3 ECG of F ... 2 ... ears before operation (A) and ... time of operation (B

who died on th thirty fifth postoperative day brought our over all postoperative mortal ty rate for the followed group to 13 per cent

In the other 34 patient the cl nical re sult based upon an improvement in functional capacity accordin to the New York Heart Association classification were con idered to be ex ellent in 1 an l g l in 13 On patient wa only sl htly im proved The other 3 patients had nitial benefit but symptoms recurred partially in 2 patient after 3 an l years where the third patient returned to preoperative status 3 years after operation There was one instance of postoperative acute rheumatic fever whereas 5 patients presented a history of afebrile arthralgia. The auscultatory findings remained unchanged in approximately 50 per cent of the patients who were followed in the other patients a diminution in the pulmonic second sound and in the diastolic apical rumble was noted. In 4 patients a nonradiating Grade 2 systolic apical murmur appeared In one patient who did not experience a lasting improvement after operation there was an increased intensity of the pulmonic second sound and of the diastolic rumble and a Grade 4 apical systolic murmur appeared The auscultatory behavior was judged solely from a comparison of preoperative and postoperative clinical notes, since phonocardiographic studies were not performed routinely

Late postoperative electrocardiographic tracings were available for comparison with preoperative records in 23 patients. In 20 of these the preoperative ECG showed evidence of right ventricular hypertrophy which decreased or disappeared completely in 15 patients (one of whom had developed atrial fibrillation on the fifth postoperative day) and which persisted unchanged in 5 Of the 3 patients who had no preoperative evidence of right ventricular hypertrophy the postoperative tracing remained unchanged in 2, and in 1 the ventriculogram was not modified but the rhythm changed from sinus to atrial fibrillation years after operation

Postoperative radiographic studies were made in 22 patients the findings remained unchanged in 12 whereas in 9 the heart size was found to be reduced and in one slightly increased

Discussion

The low incidence of rheumatic fever in children under 6 years of age is attested to by the rarity of mitral stenosis in childhood In our 54 patients who represent approximately 3 per cent of all cases of mitral stenosis observed at th clinic in only one was there a history of rheumatic fever at 5 years of age and in another at 6 years f age

If we assume the first episode of rheu

matic fever as being the one responsible for the endocarditis and hence for the valvular lesion noted at the time of admission it is evident that in many cases the stenosis must have developed quite rapidly. In fact, the time interval between the first known attack of rheumatic infection and the onset of subjective symptoms in our group averaged 2 years with a minimum of 6 months. This average of 2 years is the minimal time considered by most authors as necessary for the development of a sufficient degree of stenosis to produce subjective and objective symptoms.[3, 22, 23] White[23] states that the anatomic alterations at the onset consist of valvular insufficiency and that the murmurs present at the mitral valve area in the first year after rheumatic fever are to be attributed to dilatation of the left ventricle due to myocarditis rather than to valvular deformation. Our data do not seem to fully confirm these assertions, as demonstrated by the rapidity with which a serrated stenotic mitral valve is capable of developing in childhood. In fact, in several cases, less than a year was sufficient for the establishment of valvular narrowing and for the latter to produce significant clinical and hemodynamic disturbance. The case of Patient A.L. is an example of this rapid deterioration as illustrated in the successive electrocardiographic tracings taken 2½ years and a few days prior to operation (Fig. 3).

Mitral stenosis in childhood presents some characteristics peculiar to this group and differs somewhat from the disease as seen in the adult. In order to illustrate these differences we have compared our present group with a series of 400 older patients studied at this Institute.[24] It is to be noted that the latter group comprises 23 of the younger patients. However such a number is not large enough to affect the percentage values representing the adult patients. The greater incidence of the disease among females is seen in both groups, 68.5 per cent in children and 62.5 per cent in adults. In children the subjective symptomatology is more homogeneous than in the adults. The most frequent complaint and often the only one, is that of exertional dyspnea. The functional limitation is important: many patients are classified in Class IV, none in Class I, only one (not operated on) in Class II. Acute pulmonary edema and hemoptysis were quite frequent, whereas peripheral emboli did not exist in this group. The electrocardiographic findings were also characteristic with respect to the adult, especially for the low incidence of atrial fibrillation. There was a higher frequency of marked

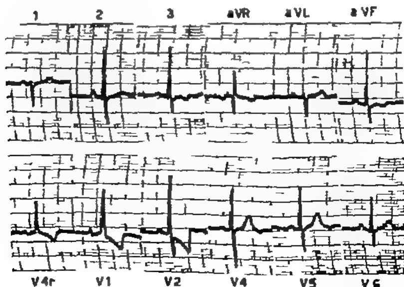


Fig. 4. ECG in a case showing high degree of right ventricular hypertrophy.

right ventricular hypertrophy in the younger patients with a tendency to very high voltage of the R wave in Leads V_{3R} and V_1 (Fig. 4). In regard to the radiographic findings, a marked degree of cardiac enlargement was less often seen in the children. The cardiac silhouette was found to be only moderately increased in the majority of cases. In particular, we did not observe in the younger patients the marked dilatation of the left atrium which is often seen in adults, a finding emphasized by Soulié and associates.

The hemodynamic data in this group were markedly abnormal. There appeared to be a greater tendency for extreme degrees of pulmonary hypertension at this age. In most instances this was due mainly to the elevated left atrial pressure; in fact, the pulmonary venous capillary pressure was always quite high, whereas the pulmonary arteriolar resistance was only moderately elevated when compared to the total pulmonary resistance. This indicates that the hypertension is due primarily to the mechanical factor of obstruction to flow produced by the stenotic valve and probably to functional precapillary vasoconstriction, whereas pulmonary arteriolar anatomic changes have not as yet assumed an overwhelming importance.[1] This fact is confirmed by the rapidity with which the pulmonary hypertension and total resistance decrease in the majority of patients after the obstructed valve has been opened surgically, returning at times to normal values. In the adults with marked degrees of pulmonary hypertension a far greater length of time is usually necessary because of the longer period of time required to bring about the regression of factors of vasoconstriction, both anatomic and functional, of the pulmonary vascular bed. Fig. 5 shows a section of lung tissue removed at the time of operation in Patient S.D. There is evident thickening of the media of a pulmonary arteriole with narrowing of the lumen which, however, remains patent. The intima is apparently intact. In this patient the preoperative pulmonary arterial pressure was 140/75 mm. Hg and the resistance was calculated to be 1,072 dynes sec. cm.$^{-5}$ One month after operation the pressure had fallen to 45/18 mm. Hg, and the resistance to 464 dynes sec. cm.$^{-5}$ Fig. 6 shows a section of lung tissue from an adult patient with a pulmonary arterial pressure of 75/40 mm. Hg and a total pulmonary resistance of 1,141 dynes sec. cm.$^{-5}$ The graver anatomic alterations of the pulmonary arteriole shown in the section are apparent, with



Fig. 5. Lung biopsy of patient S.D. showing hypertrophy of pulmonary arteriole with patent lumen and intact intima (Van Gieson stain).

complete occlusion of the lumen resulting from hypertrophy and hyperplasia of the vessel wall

What is the possible explanation for the particular behavior of mitral stenosis in childhood? Rheumatic fever is notoriously a chronic insidious disease in which the clinical manifestations may be only slightly apparent, but which is capable of producing progressive damage to the cardiac structures, in particular to the myocardium Thus, in the adult patient the hemodynamic equilibrium and the electrocardiographic and radiographic modifications are influenced not only by the mechanical obstruction and its consequences but also by the sequelae of myocardial disease This combination results in a markedly increased heart size due more to dilatation than to hypertrophy with atrial fibrillation a pulmonary arterial pressure only moderately elevated and a reduced cardiac output all of which are seen more frequently in the adult patient. In children the duration of rheumatic infection is naturally shorter and the clinical and objective findings appear to indicate that the heart reflects above all the results of the localized valvular endocarditis. The heart is enlarged but usually only moderately so the rhythm is always sinus, and the ECG quite often presents evidence of marked right ventricular hypertrophy These elements indicate the prevalence of the mechanical factor over the myocardial factor This is in agreement with the opinion expressed by Bradlow and Crawshaw [6] who have stressed that the dangers brought about by the stenosed valve are more important than the consequences of the rheumatic disease in itself especially at this age. It may well be that a left atrium only slightly enlarged with a wall of normal tonicity because the histologic lesions of rheumatic activity have not produced extensive fibrosis contracting under the stimulus of normal sinus rhythm would be able to react to the valvular obstruction by a marked increase in pressure which is freely transmitted upstream resulting in high degrees of pulmonary hypertension Furthermore, the relatively healthy ventricular myocardium permits at this stage a better function which results in the maintenance of a normal cardiac output.

We have seen how in children the pulmonary arteriolar resistance seems to be somewhat lower in comparison with the total pulmonary resistance, than that usually seen in adult patients with tight mitral stenosis, which would imply a lesser degree of precapillary involvement. If on



Fig 6 Lung biopsy from an adult patient with mitral stenosis, showing complete obliteration of pulmonary arteriole (Van Gieson stain).

the one hand this represents a favorable situation that enables the rapid return to normal of pulmonary hemodynamics after operation, it is on the other hand the cause of the high l ability of these patients who lack the protective barrier at the arteriolar level. Four of our patients with marked hypertension died during an episode of acute pulmonary edema before they could be brought to operation and in 2 of these the fatal episodes appeared a few hours after cardiac catheterization. Thus the latter procedure carried in our series a higher mortality than did operation itself.

In view of all these considerations it is evident that in this childhood group the mechanical and functional factors prevail and that the disease is characterized by a rapidity of evolution and by a severe degree of hemodynamic alteration. We believe therefore that the indications for early valvotomy are indisputable and should not be set aside because of the hypothetical fear of recurrence of the rheumatic process or of the deleterious effects of subclinical rheumatic activity. In this last respect we must recall that in 58 per cent of our patients the sedimentation rate was elevated. No study was made of the left atrial appendage for histologic signs of rheumatic activity. Needless to say, operation should be postponed in the face of clinical and laboratory evidence of acute endocarditis or myocarditis.

The advantages of valvotomy at this age are confirmed by the immediate and remote results. At operation the finding of a tight fibrotic valve and the absence of calcifications permitted in a large percentage of patients a satisfactory result with a rather low incidence of postoperative insufficiency. The rarity of atrial thrombi explains the absence of preoperative embolic complication in our group. The mortality of zero per cent indicates that the surgical intervention is very well tolerated even in those patients who are seriously incapacitated. The long term mortality rate (13 per cent of 38 patients followed) was higher than that observed in the group of 400 adults (6 per cent). In one patient death occurred 5½ years after operation; it was attributed to chronic glomerulonephritis and was therefore not directly related to the patient's cardiopathy. Of the other 3 patients who died after 1, 2, and 5 years, respectively, the condition at the time of operation was grave with evident clinical manifestations of right heart failure (peripheral edema, hepatomegaly, jugular venous distention). As for the patient who died on the thirty-fifth postoperative day, autopsy revealed an aortic insufficiency which apparently had been underestimated in the evaluation for operation. The long term results may be considered to be very satisfactory. In fact, in 79 per cent of our patients the clinical result on an average of 4 years after discharge was considered to be excellent or good, whereas a similar result was obtained in 70 per cent of the adult group over a period of 4½ years. This success could be anticipated from the observation of the rapid and favorable hemodynamic response to operation. In the less fortunate patients the recurrence of symptoms after a prolonged period of improvement was certainly due in one to restenosis with tricuspid insufficiency. In one other, after a 4 year period of benefit, the clinical deterioration was coincident with the appearance of atrial fibrillation, indicating presumably a spontaneous evolution of the rheumatic disease.

It is important to note the very low incidence of frank rheumatic reactivation after operation, whereas 31 per cent of the adult group have suffered definite recurrence of rheumatic fever. It appears, therefore, that the fear of the harmful influence of continuing rheumatic activity is unfounded, for it did not affect the results neither as a systemic disease nor as a cause of restenosis. In this regard our experience is in accord with that of Brest and associates,[7] Bradlow and Crawshaw, Borman and associates, Angelino and associates, Cibert-Querulté and associates, and Soulié and associates.[3] The latter authors, however, offer two objections to the indication for mitral commissurotomy in childhood: a higher operative mortality rate (17 per cent in their series) and the uncertainty of long term results. Our findings would appear to disprove this impression. In agreement with Lurie and Shumacker,[28] we believe that operation is contraindicated only in cases of asymptomatic mitral stenosis in the presence of

acute rheumatic fever and when there are clinical and objective findings of overt cardiac failure. In other cases, commissurotomy would appear to interrupt the grave and rapidly progressive devolutionary course of the disease which seems to characterize mitral stenosis in childhood.

Summary

Fifty-four patients with mitral stenosis aged 8 to 15 years, are reported on. The symptomatology was constantly quite severe and all patients except one belonged to functional Classes III and IV. The electrocardiogram showed normal sinus rhythm in all, left atrial hypertrophy in 74 per cent, and right ventricular hypertrophy in 63 per cent. Radiologic heart size was only moderately increased in most cases. Catheterization of the right side of the heart performed in 27 patients revealed a high percentage of marked pulmonary hypertension arteriolar resistance being relatively low in respect to total pulmonary resistance. Two patients were discharged, one because of acute endocarditis, the other because of normal hemodynamic data. Four patients died before operation. The other 48 patients underwent mitral valvotomy. At operation the valve was found to be markedly stenotic in most cases. There were no valvular calcifications. Valvotomy was estimated to be satisfactory in 96 per cent of the cases. In 4 patients, slight to moderate insufficiency was created. There was no operative mortality; one patient died 35 days after operation.

Late postoperative clinical information was available in 38 patients, with a duration of follow-up from 1 to 8 years. Four patients died, after 1, 2, 5, and 5½ years. As for the other 34 patients, the clinical result was excellent in 17 and good in 13. One patient showed only slight improvement. After a period of initial benefit in 3 patients, there was a recurrence of symptoms, complete in one due to restenosis, partial in the others. The ECG showed regression of right ventricular hypertrophy in most cases, whereas the radiologic appearance remained mostly unchanged. There was only one instance of frank rheumatic reactivation.

It is believed that mitral commissurotomy is clearly indicated in the childhood group, except in cases of acute carditis and/or overt cardiac failure.

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Left ventricular–right atrial communication in complete transposition of the great vessels

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Left ventricular–right atrial communication, an uncommon malformation, has heretofore been described as either an isolated condition or one associated with cardiac malformations in which the fundamental anatomic arrangement allows full saturation of the systemic blood.

Among 60 cases of complete transposition of the great vessels studied pathologically from our institutions, a ventricular septal defect was present in 22. In three of these a peculiar ventricular septal defect was found which resulted in a left ventricular–right atrial communication and did not result in a communication between the left and right ventricles. Pathologic findings were available for all three cases but clinical data were obtainable for only two (Cases 1 and 2). In these two there were distinct clinical manifestations which marked them as different from other cases of complete transposition of the great vessels recently studied by us.

One patient (Case 1) died after surgical repair was attempted. It is noteworthy that any attempt at complete surgical correction of this type of ventricular septal defect will be complicated by the malformed tricuspid valve, which in each of the three cases reported herein was intimately connected with the abnormal communication.

Because the clinical findings depend upon the anatomic arrangements, the pathologic features in the three cases will be reported first.

Pathologic features

All three specimens showed complete transposition of the great vessels and an abnormal communication between the left ventricle and right atrium (namely, a left ventricular–right atrial communication).

External examination revealed the two great vessels to be transposed; the aorta took origin from the right ventricle and

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Fig. 1. Three [illegible] of complete [illegible] posit[illegible]n of the gre[illegible]t [illegible] with left [illegible]entricular-right [illegible]trial communi[illegible]cation. *Upper left.* Case 1. Right [illegible] of heart. There is [illegible] left at the junction of the septal and [illegible]terior leaflet of the tricuspid [illegible]. The edges of [illegible] are knobbed and rolled. The probe is [illegible] the communication between the right [illegible]trium (R.A.) and the left [illegible]entricle. (R.V., Right [illegible]entricle.) *Upper right.* Case 1. Left [illegible]entricular view. The [illegible]entricular septal defect ([illegible]) lies below the pulmonary [illegible]. The posterior margin of the defect is formed by the conjoined [illegible] of the [illegible]terior and septal tricuspid leaflet. (L.V., Left [illegible]entricle.) *Center left.* Case 2. View of right [illegible]trium and right [illegible]entricle (R.V.). There [illegible] left in the tricuspid [illegible] similar to that in Case 1. The probe represent[illegible] the site of communication between the right [illegible]trium and left [illegible]entricle. *Center right.* Case 2. Left [illegible]entricle (L.V.) and pulmonary trunk (P). The [illegible]enter of the defect ([illegible]) lies below the junction of [illegible] and posterior cusps of the pulmonary [illegible]. Element[illegible] of the tricuspid [illegible] protrude through the defect into the left [illegible]entricle. *Lower left.* Case 3. Right [illegible]entricle (R.V.) and left [illegible]tricuspid [illegible]. The chordae of the septal leaflet are not as intimately related to the posterior edge of the ventricular septal defect [illegible] Cases 1 and 2 but are connected to small papillary muscles in the [illegible]entricular septum. *Lower right.* Case 3. Left [illegible]entricle (L.V.) and pulmonary [illegible]. The [illegible]entricular septal defect [illegible] situated beneath the pulmonary [illegible] and [illegible] prominen[illegible] of the [illegible]entricular septum [illegible] protrude[illegible] to the left ventricular [illegible] and [illegible] obstruction in this region.

the pulmonary trunk took origin from the left ventricle The aorta was anterior and to the right of the pulmonary trunk.

All specimens showed dilatation and hypertrophy of both ventricles, and dilatation of the atria The mitral valve and the venous connections with the atria (including the systemic veins, coronary sinus, and pulmonary veins) were normal

A communication between the greater and lesser circulations existed as a patent ductus arteriosus (1 mm internal diameter) in one case (Case 3) There was a valvular competent patent foramen ovale in each specimen The largest avenue by which blood could cross from one side of the circulation to the other was by way of the peculiar ventricular septal defect which resulted in the left ventricular–right atrial communication in each instance

From the right ventricular view in each specimen the ventricular septal defect was located posteroinferior to the crista supraventricularis and below the papillary muscle of the conus (Fig 1 *upper center* and *lower left*) there was a cleft in the tricuspid valve at the junction of the septal and anterior leaflets. In two (Cases 1 and 2) the anterior edge of the septal leaflet of the tricuspid valve was adherent to the posterior edge of the ventricular septal defect resulting in a communication from the left ventricle to the right atrium (Fig 1 *upper* and *center left*) Here, the edges of the septal and anterior tricuspid valve leaflets were knobby rolled and appeared to render the tricuspid valve incompetent In Case 3 the chordae to the septal leaflet were not intimately related to the posterior edge of the ventricular septal defect but were attached to short papillary muscles which in turn adhered to the ventricular septal wall (Fig 1 *lower left*) The posterior aspect of the anterior leaflet of the tricuspid valve showed a roughened corrugated appearance and adhered by short chordae to the anterior margin of the ventricular septal defect

From the left ventricular aspect the center of the defect in each case lay essentially below the right pulmonary cusp (Fig 1 *upper center* and *lower right*) The posterior margin of the defect was formed by the conjoined elements of the septal leaflet of the tricuspid valve and of the anterior leaflet of the mitral valve In addition elements of the septal leaflet of the tricuspid valve protruded into the left ventricle through the defect In Case 3

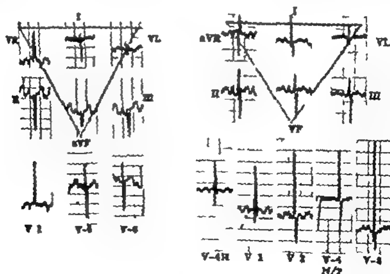


Fig 2 The electrocardiograms in two cases of left ventricular–right atrial communication with complete transposition of the great vessels. *Left* Case 1 (4 months old). *Right* Case 2 (3 months old). Each tracing shows the features commonly observed in the electrocardiogram of patients who have malformations of the A-V commune type (see text). N/2 = half standardization.



Fig 3 C se 1 (4 months old) Thoracic roentgenograms. *Left.* Anteroposterior view shows an enlarged ardiac shadow ssuming the typical egg-shaped contour commonly observed in omplet t position. The superior mediast um is narrow There is evidence of "increased pulmonary sculanty *Right* Lateral iew show left atrial enlargement as evidenced by a posteriorl displaced barium filled esophagus.

a zone of obstruction to left ventricular outflow was located below the defect as a protrusion of the muscular part of the ventricular septal defect into the outflow tract (Fig 1 *lower right*)

Clinical features

Both patients on whom clinical data were available were boys one was 5 months of age when he died after surgical repair was attempted (Case 1) the other died at 3 months of age as a result of congestive cardiac failure (Case 2) The patient on whom no clinical data were available was 5 years old at the time of death (Case 3)

At birth the infants were of full term weight and were without obvious physical deformities Both exhibited mild cyanosis within 24 hours after birth A cardiac murmur was noted at birth in Case 1 and on the fifth day of life in Case 2 In both cases congestive cardiac failure developed within the newborn period The following physical findings apply to both patient Systemic blood pressures were normal and the infant were small and thin Examination revealed a diffuse systolic thrill along the lower left sternal border a harsh holosystolic murmur which wa judged variously to be Grade 3 to 4/6 in inten ity was heard maximally along the lower left sternal border and radiated well over the entire thorax An apical dia tolic murmur of Grade 2 to 3/6 intensity was heard midway between the apical area and the fourth left intercostal space Accentuation and narrow splitting of the second cardiac sound at the second right intercostal space were noted

Electrocardiographic finding : Electrocardiographic abnormalities were present both in Case 1 and Case 2 Although no conduction disturbances were present the P waves indicated left atrial enlargement in each

The mean QRS axis was of the left axis



Fig 4 C se 2 (3 month old). Anteropo terior thoracic roentgenog m howing egg-shaped ardiac ilhouett with increased pulmonary sc larity

deviation type −125 degrees in Case 1 and −65 degrees in Case 2 By vectorial analysis, the QRS loop in the frontal plane was inscribed counterclockwise and oriented superiorly to the isoelectric line in both

Features of right ventricular hypertrophy of the systolic (pressure) overload type were evident in Case 1 (Fig 2 *left*) and combined ventricular hypertrophy was evident in Case 2 (Fig 2 *right*)

Roentgenologic findings Thoracic roentgenograms in Cases 1 and 2 were also comparable. Both showed cardiac enlargement (Figs. 3 and 4) the cardiac shadow was egg shaped a configuration commonly seen in complete transposition. The pulmonary vasculature was prominent but the superior mediastinum was narrow and no shadow of the pulmonary artery could be seen Signs of left atrial enlargement were present in each instance

In one patient (Case 1) venous angiocardiography was performed The aorta arose anteriorly from the right ventricle and the major portion of the contrast media was ejected into the systemic circulation during the first few seconds of study only a scant amount of recirculated contrast media passed into the left side of the heart. Thus this study did not reveal any signs that could have led to a recognition that a communication existed between the left ventricle and the right atrium.

Comment

According to the pathologic material recently studied by us, the incidence of complete transposition of the great vessels with coexisting left ventricular–right atrial communication was found to be relatively high of 60 cases with complete transposition three (5 per cent) had the subject defect. These three comprise 13 per cent of the 22 cases which were found with an associated ventricular septal defect

As judged by our two cases in which clinical data are available the clinicopathologic manifestations of left ventricular–right atrial communication with complete transposition of the great vessels yield two noteworthy features. These are the auscultatory and electrocardiographic findings which resemble phenomena usually described for persistent common atrioventricular canal [3]

According to general experience in complete transposition of the great vessels with ventricular septal defect a loud isolated holosystolic murmur is not unusual [4] The combination of a loud holosystolic murmur and diastolic murmur however is unusual Although the murmurs in our two cases are similar to those found in persistent common atrioventricular canal without transposed great vessels,[4] we do not understand completely the mechanism involved in the defect herein described.

The systolic murmur in our cases may originate primarily from the flow through the ventricular septal defect or as the result of an incompetent tricuspid valve. Both mechanisms could be operative

In persistent common atrioventricular canal the diastolic murmur is presumably the ultimate result of the underlying left to-right shunt at the atrial level which culminates in an excessive forward flow of blood across the tricuspid valve [4] In addition Paul[7] attributes part of this diastolic murmur to certain abnormalities of the left atrioventricular valve. The diastolic murmur found in our two cases may also have originated from excess flow across the tricuspid valve. This excess flow could have resulted from a large volume of blood being directed into the right atrium during systole both from the left ventricular–right atrial communication and from regurgitant flow through an incompetent tricuspid valve

Additional components of the diastolic murmur in our two cases may have been contributed by an increased flow of blood at the normally formed mitral valve.

Certain electrocardiographic features of our cases are shared with persistent common atrioventricular canal These include left axis deviation a counterclockwise QRS loop in the frontal plane deviated far above the isoelectric line, and complexes in precordial leads compatible with right or combined ventricular hypertrophy

In an electrocardiographic analysis of 52 cases of complete transposition of the great vessels, a ventricular septal defect was present in 26. Among these 26, some degree of left axis deviation was observed in four cases two showed mild degrees of



Fig. 3 Case 1 (4 month old). Thoracic roentgenograms. *Left*: Anteroposterior view shows enlarged cardiac shadow assuming the typical egg-shaped contour commonly observed in complete transposition. The superior mediastinum is narrow. There is evidence of "increased pulmonary vascularity. *Right*: Lateral view shows left atrial enlargement as evidenced by posteriorly displaced barium-filled esophagus.

a zone of obstruction to left ventricular outflow was located below the defect as a protrusion of the muscular part of the ventricular septal defect into the outflow tract (Fig. 1 *lower right*).

Clinical features

Both patients on whom clinical data were available were boys: one was 5 months of age when he died after surgical repair was attempted (Case 1), the other died at 3 months of age as a result of congestive cardiac failure (Case 2). The patient on whom no clinical data were available was 5 years old at the time of death (Case 3).

At birth, the infants were of full term weight and were without obvious physical deformities. Both exhibited mild cyanosis within 24 hours after birth. A cardiac murmur was noted at birth in Case 1 and on the fifth day of life in Case 2. In both cases, congestive cardiac failure developed within the newborn period. The following physical findings apply to both patients: Systemic blood pressures were normal and the infants were small and thin. Examination revealed a diffuse systolic thrill along the lower left sternal border; a harsh holosystolic murmur, which was judged variously to be Grade 3 to 4/6 in intensity, was heard maximally along the lower left sternal border and radiated well over the entire thorax. An apical diastolic murmur of Grade 2 to 3/6 intensity was heard midway between the apical area and the fourth left intercostal space. Accentuation and narrow splitting of the second cardiac sound at the second right intercostal space were noted.

Electrocardiographic findings: Electrocardiographic abnormalities were present both in Case 1 and Case 2. Although no conduction disturbances were present, the P waves indicated left atrial enlargement in each.

The mean QRS axis was of the left axis



Fig. 4 Case 2 (3 month old). Anteroposterior thoracic roentgenogram showing an egg-shaped cardiac silhouette with increased pulmonary vascularity.

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Electrocardiographic intervals during the first week of life

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The electrocardiographic findings in the neonate have largely proved disappointing in diagnosis. Attention has been directed primarily toward establishing normal standards for deflections and describing changes in electrical axis and T waves.[1-6] Intervals, on the other hand, have been dealt with for the most part summarily or not at all.[7] The classification of infants from birth to 1 week of age or more into a single group and the paucity of serial investigations instituted immediately after birth have no doubt also been partly responsible. It seems reasonable, however, to assume that the vast circulatory changes which occur at birth are mirrored to some extent in the electrocardiogram. There appears to be some evidence in favor of this assumption, for in a recent study of healthy full-term infants both P wave duration and the P-R interval were considerably prolonged, primarily in infants less than 1 hour old.[8]

The present investigation was undertaken to determine whether other intervals are similarly prolonged. Serial electrocardiograms were taken on 68 healthy full-term infants on the first, second, third and fifth or sixth days of life. An attempt was made to examine the infants as shortly after birth as possible. The Q-R time, QRS and Q-T intervals and Q-T were measured.

Method

All electrocardiograms were taken on a 4-channel jet writer by the author with the help of an assistant. The machine was standardized to produce a deflection of 1 cm with the introduction of 1 mv. into the circuit. A paper speed of 100 mm. per second was used to increase the accuracy of measurement of intervals. The smallest unit of measurement was 0.005 second. The heart rate was generally measured on strips of 30 cm. Measurements of all QRS and Q-T intervals in a single strip were made in Lead II for purposes of comparison with most available data, as well as in the precordial leads and the maximum value in both were recorded. The Q-R time was measured in Leads V_1 and V_6 from the beginning of QRS to the peak of the R wave. All measurements were made with a magnifying lens of 5X. The Q-T was calculated by the application of Bazett's formula.

Infants were either asleep or quietly sucking a pacifier at the time of examination. Every effort was made to disturb them as little as possible and no records were taken when they became restless. Maternal anesthesia and analgesia at the time of delivery were minimal to none. All infants were auscultated and chest roentgenograms were recorded for all. None showed clinical evidence of heart disease.

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Results

The infants were divided into four groups according to age at the time of initial examination Group I—17 infants, 15 to 30 minutes old Group II 21 infants, 35 to 60 minutes old Group III—13 infants 65 minutes to 4 hours old and Group IV—17 infants, 4½ to 18¾ hours old All infants had four examinations each and 42 of the 68 were females.

Q-R time. On initial examination infants in Group I had a Q R time in Lead V of 0.01 to 0.035 sec (3 had a value of 0.03 to 0.035 sec) with a mean of 0.020 sec. whereas infants in Group IV had a range of 0.01 to 0.025 sec. with a mean of 0.017 sec. This difference was almost significant ($p < .10$) By the third day the respective means were 0.017 and 0.0175 sec with a range of 0.01 to 0.03 sec When the groups were combined and analyzed the maximum value appeared to decrease with age on the first day of life That is, after 2 hours no value exceeded 0.025 sec and after 5 hours the maximum recorded was 0.02 sec. From the second to the fifth days, the number of infants with a value of 0.01 sec decreased significantly from 12 to 1 4 per cent ($p < .05$)

In Lead V₆, the groups were combined since no significant differences were present When the Q-R times on the first and fifth days of life were compared a value of 0.03 sec. was found in 15 per cent initially and in 1 4 per cent subsequently ($p < .001$) Similarly a Q-R time of 0.015 sec or less was found in 27 per cent which figure then decreased to 12 per cent ($p < .05$) With increasing age therefore a significant decrease occurred in both the minimum and maximum Q-R times. The difference between the distribution of Q-R values on the first and last examination was also found to be highly significant ($p < .001$) (Table I)

Table I Effect of age on Q-R time in Lead V

Day	Number	Q-R time (sec) Lead V		
		0.015 or <	*0.02-0.025*	*0.03 or >*
First	67	17	40	10
Fifth or sixth	68	8	59	1

By the end of the first week of life, most infants have Q-R time of 0.02 to 0.025 sec.

The range in values cannot be compared with those reported by Ziegler[1] because he measured the time of onset in the precordial leads from the beginning of QRS in simultaneously recorded Lead I The maximum value found by Michaelson was 0.03 sec. but the infants were 30 minutes old, or more and he failed to state in which leads this interval was measured

Individual differences in Q-R time in Leads V₁ and V were then determined On the first day a Q-R time in Lead V₁ greater than that in Lead V was present in 41.5 per cent of the infants in Group I and in 62 per cent of those in Group IV When all 68 infants were included, this finding was present in one half of the infants on the first day and in one third of the infants on the second day Generally the differences in Q-R time in both leads were small It is noteworthy that values in Lead V are of the same magnitude as those normally found not only in older infants and children but also in adults.

QRS interval On initial examination the difference between a mean QRS interval of 0.055 sec. in infants of Group I and 0.048 sec in infants of Group IV was found to be highly significant ($p < .001$) Furthermore 65 per cent of the infants of Group I had a QRS interval of 0.055 sec. or more, whereas only 25 per cent of those of Group IV had values in this range. By the second day of life, the mean value for the youngest infants was 0.049 sec., and for the oldest it was 0.050 sec. In other words, no change occurred in the percentage of infants in Group IV with a value of 0.055 sec. or more (Table II)

Similar values with the exception of those for Group I on the first day of life, were found by Michaelson Rothfeld[1] (who included all infants from 1 hour to 5 days in a single group) and Furman and Halloran The latter analyzed their data from the first month of life and found an interval of 0.055 sec. or more in 28 per cent. On the other hand a far wider range was reported by Ziegler During the

first 24 hours of life the range was 0.04 to 0.10 sec. and from 1 to 7 days it was 0.04 to 0.08 sec. with a mean of 0.056 sec. Coleman[13] in a study of infants from 2 weeks to 1 year of age also found that Ziegler's mean QRS values were higher. Although conduction disturbances in the neonate are uncommon, they do occur.[6] In the absence of evidence to the contrary it seems likely that a few tracings with bundle branch block were included and these account for the discrepancy.

Because the change in QRS interval appeared to parallel that previously described for P and P-R intervals, the relationship between these intervals and the QRS interval was analyzed. On the first day of life maximum values of both P wave duration and QRS interval occurred in 6 infants of Group I and in none of Group IV. On the second day no infant in either group had this combination. Likewise, maximum values of both P-R and QRS intervals were encountered in 8 infants of Group I but in none of Group IV. On the second day of life this finding was present in 1 infant in each group (Tables III and IV). It would appear, therefore, that in some instances the same factor which is operative in prolongation of P and P-R intervals also influences QRS duration. By means of scattergrams the interval was found not to be influenced by heart rate.

Since both lateral and posteroanterior roentgenograms of the chest had been taken on all of these infants on the first and fifth or sixth days of life, it was thought of interest to relate heart volume employing the method described by Lind[7] to the QRS interval.

Despite a significant decrease in heart volume with age, the decrease appeared to be independent of that of the QRS interval.

Q-T interval and Q-T. As has been noted by others, the Q-T interval proved to be difficult to measure, especially on the first day of life when T waves are isoelectric or of low amplitude. In the precordial leads, the Q-T was generally measured in leads with a high voltage T and a more clearly distinguishable U wave.

In Lead II the mean Q-T interval decreased from 0.29 to 0.27 sec. during the first week of life ($p < .01$). Fourteen infants had an interval of 0.315 sec. or more initially, but none had values in this range at the end of the week. On initial examination in precordial leads the mean and maximum values recorded were 0.30 and 0.38 sec., respectively, with a standard deviation of 0.033 sec. The incidence of shorter Q-T intervals was significantly greater in infants who were more than 1 hour old. That is, an interval of 0.26 sec. or less was present in 2.6 per cent of the younger infants and in 30 per cent of the older infants ($p < .001$). Twenty-five per cent of Ziegler's cases were in this range, which would again suggest that the infants whom he studied were more than 1 hour old.[11] An interval of 0.305 sec. or more was present in 35 per cent of the infants on the third day and in only 6 per cent by the fifth or sixth days of life ($p < .001$). In other words, a highly significant decrease in maximum values occurred with age.

The range and means during the first 24 hours of life correspond almost exactly to those of Ziegler. Since he combined all subsequent readings during the first week of life, comparison is limited, but the range is similar although the means in this study are slightly higher.

But when should the Q-T interval be considered prolonged in newborn infants? The maximum value recorded by Ziegler in infants between 1 week and 3 years of age was 0.30 sec. The constancy of this value over such a long period would appear to justify its use. In this study, therefore, 31 infants had a prolonged Q-T interval in precordial leads on the first day of life in contrast to 4 infants at the end of the week.

Individual measurements of the Q-T interval were plotted against heart rate. As shown in Table V, an inverse correlation is present in that more rapid heart rates were associated with shorter intervals. When the Q-T was corrected for rate (Q-T$_c$), a significant decrease in maximum values was again noted during the first week of life (Table VI).

Since there appeared to be some relationship between maximum values of the QRS and the P and P-R intervals, the Q-T interval was plotted against these intervals. In this instance no relationship

Table II Relationship between age and QRS interval on the first and second days of life

Age on initial examination	Day	Number	QRS interval (sec.)			S.D
			Minimum	Mean	Maximum	
30 minutes or less	First	17	0 045	0 055	0 07	0 0057
	Second	17	0 04	0 049	0 06	0 0049
4½ hours or more	First	16	0 04	0 048	0 055	0 0049
	Second	17	0 045	0 050	0 06	0 0040

Significantly longer intervals are encountered in infants 30 minutes old or less on initial examination.
S.D = Standard Deviation.

Table III Relationship between P duration and QRS interval on the first and second days of life

Day	P duration (sec)	30 minutes old or less			4½ hours old or more		
		Number	QRS interval (sec)		Number	QRS interval (sec)	
			0.05 ≦	0.055 ≧		0.05 ≦	0.055 ≧
First	0 06 or <	17	1	5	16	9	3
	0 065–0 085		5	6		2	0
Second	0 06 or <	17	9	5	17	10	4
	0 065–0 085		3	0		3	0

Maximum values of both intervals on the first day of life occurred only in infants 30 minutes old or less.

Table IV Relationship between P R and QRS intervals on the first and second days of life

Day	P R interval (sec)	30 minutes old or less			4½ hours old or more		
		Number	QRS interval (sec)		Number	QRS interval (sec)	
			0.05 ≦	0.055 ≧		0.05 ≦	0.055 ≧
First	0 105 or <	17	0	3	16	7	4
	0 11 or >		6	8		5	0
Second	0 105 or <	17	9	3	17	7	3
	0 11 or >		4	1		6	1

Maximum values of both intervals on the first day of life occurred only in infants 30 minutes old or less.

Table V Distribution of cases according to heart rate and Q-T interval in Lead II on the first and fifth or sixth days of life

Q-T interval (sec.)	First day			Fifth or sixth days		
	Heart rate			Heart rate		
	110-149	150-174	175-210	110-149	150-174	175-210
0.21 -0.255	0	9	1	0	8	8
0.26 -0.31	16	23	3	13	32	7
0.315-0.38	12	2	0	0	[illegible]	0

By the end of the first week no infant had a Q-T interval that exceeded 0.31 sec.

was found which would suggest that some other factor is involved

Comment

The data indicate that, contrary to the opinion expressed by Groedel and Miller,[8] significant changes do occur in these intervals during the first week of life. Low serum potassium may result in prolongation of P-R, QRS, and Q-T intervals, as well as in low T waves, but these changes are not specific for this condition. In newborn infants, however, the levels of serum potassium are elevated at birth and on the first day of life.[24] The important factor is the ratio of concentration of potassium inside the myocardial cell to that in the interstitial spaces surrounding this cell. During rapid changes in the level of serum potassium the extracellular tissue concentration may lag behind the level in the serum. Imbalance of other electrolytes may also affect the serum concentration.[25]

The QRS interval is relatively prolonged during the first half hour of life and appears to be influenced in some instances by the same factor that influences the P and P-R intervals. Transient prolongation of the P-R interval is often considered to be of vagal origin, presumably the result of increased potassium permeability of conduction tissue, but the degree of vagal tone in the neonate is still unknown. Asphyxia independent of vagal activity can also produce prolongation of this interval, and during the first hour of life low oxygen saturation is often present. Furthermore, anoxemia increases the sensitivity of the heart to vagal action. There is also evidence that the length of the QRS interval is related to the weight of the ventricles,[22] although in this study no relationship was found between the interval and heart volume. But many electrocardiographic patterns attributed to hypertrophy of a ventricle are partly, if not entirely, due to conduction defects such as bundle branch block.[23] For the most part notching was uncommon in precordial leads, but this does not exclude a conduction defect. However, the incidence of notching in right precordial leads did increase with age.

The Q-R time is dependent in some measure on the relative thickness of the underlying ventricle. This interval is prolonged in conduction disturbances and in ventricular hypertrophy. Diastolic overload may also modify the activation process

Table VI Distribution of cases according to Q-T during the first week of life

Day	Q-T (Lead II) = K √ cycle length sec			
	0.33-0.42	0.43-0.48	0.49-0.54	S.D.
First	20	33	13	0.015
Second	14	42	11	0.018
Third	16	48	3	0.015
Fifth or sixth	29	38	3†	0.015

*Maximum 51
†0.49 sec.

and result in a delayed Q-R time over the affected ventricle.[24] At birth the volume of the left ventricle is approximately three quarters that of the right ventricle.[25] With expansion of the lungs, the load on the left ventricle becomes considerably greater and is increased still further by a patent ductus. Although the length of time during which significant left-to-right shunting through a ductus occurs is still under debate, several investigations suggest that by the end of the first week of life this shunt has become insignificant.[27,28]

There is significant error inherent in measurement of the Q-T interval especially in the neonate although greater reliance can be placed on measurements made in precordial leads when T waves are low or isoelectric. Furthermore, a number of conditions influence its duration but among these is ventricular overload. It does not seem unreasonable to suppose that this may account in part for the highly significant decrease with age in both the Q-R time in Lead V and the Q-T interval.

Summary

1. Two hundred twenty-two electrocardiograms were taken on 68 healthy full-term infants during the first week of life.

2. Significant changes in the length of the QRS, Q-R, and Q-T intervals occurred with age, and the mechanisms involved are discussed.

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Electrocardiographic changes in hypertrophic subaortic stenosis which simulate myocardial infarction

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Four young patients whose electrocardiograms show abnormal Q waves suggestive of myocardial infarction but in whom coronary artery disease has not been demonstrated have recently come to our attention. Two have hypertrophic subaortic stenosis and the other 2 are suspected of having the same disturbance. Our experience, together with recent reports which deal with hypertrophic subaortic stenosis, suggest that this diagnosis may be suspected in young people with this particular electrocardiographic abnormality.

Case reports

Case 1. In the 2 years before hospitalization, this 19-year-old man had twice experienced sharp pain in the left side of the chest; this had occurred after heavy lifting and was aggravated by deep breathing, coughing, and exertion. Physical findings 14 months before admission included pectus excavatum, normal-sized heart, and systolic murmur. The electrocardiogram at this time showed the abnormalities seen in Fig. 1. It showed no evolutionary changes, and an exercise tolerance test produced no additional abnormalities. Determinations of serum glutamic oxalacetic transaminase (SGOT) were 48 and 20 units. The symptoms subsided on rest alone. A diagnosis of arteriosclerotic heart disease with anterolateral myocardial infarction was made. Localized pain in the left side of the chest continued to occur on exertion, and, in the 2 weeks before admission, the patient had twice entered another hospital where the same electrocardiographic findings were noted. SGOT and cholesterol had been normal, and he was referred to our hospital for additional study. There was no history of rheumatic fever or of familial heart disease. On physical examination, the pulse was 82, and the blood pressure was 110/80 mm. Hg. The heart was normal except for a Grade 3 coarse midsystolic murmur maximal at the left sternal border in the fourth intercostal space, transmitted to the left axilla and to the neck, and a Grade 2 early diastolic murmur in the same location. Pectus excavatum was the only other remarkable finding. The vectorcardiogram agreed with the original diagnosis. A phonocardiogram confirmed the diamond shape and mid-systolic timing of the systolic murmur. The electrocardiogram remained unchanged after administration of quinidine and atropine. Other normal studies included an exercise tolerance test, coronary angiogram, determination of coronary blood flow by the nitrous-oxide technique, and ballistocardiogram. Angiography indicated a probable bicuspid aortic valve. Catheterization of the left and right sides of the heart re-

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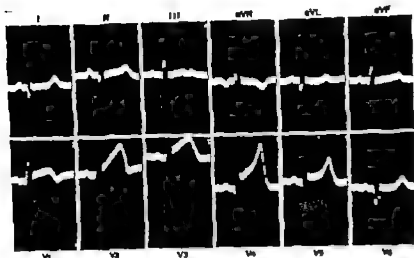


Fig. 1. Electrocardiogram of Case 1.

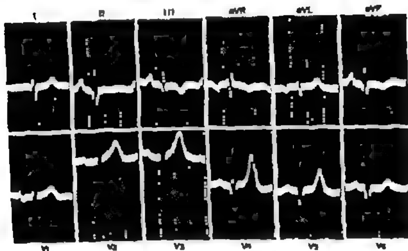


Fig. 2. Electrocardiogram of Case 2.

ealed aortic subvalvula gradient of 22 mm. Hg consistent with subaortic stenosis. The contou of the central aortic pulse showed the character istic sharp initial spike followed by prolonged, lower secondary rise.[19] The stenotic chamber was not demonstrated by entriculography. A small pressure gradient was also noted in the in- I ndibular portion of the right entricular outflow tract. The patient as discharged ithout medication and, except for easy fa igability, has remained asymptomatic.

This patient father nd 2 siblings ha normal electrocardiograms nd no cardiac murmurs. His mother whose electrocardiogram has show only incomplete right bundle branch block, has been under physicia care for fast, forceful heart action. She also has pect excu tum nd a Grade 3 coarse, mid-systolic murmur which is maximal at the low left sternal border and radiates faintly to the aortic area and neck.

Case 2. This patient, 28-year-old man, had had scarlet fever and non-specific pain in the knee joints in childhood but was well until the age of 23 when cardiac murmur wa first noted. Slight exertional dyspnea followed and in the year before admission t the hospital he complained of fatigue nd three episodes of "blackout after climbing stairs, during which he nearly fell. He lso noted occasional palpitations of the heart. Because of these ymptoms, he entered another hospital, where the ital signs were found t be normal and the blood pressure 100/60 mm. Hg. There was no cyanosis or clubbing and the lungs were clear. The cardiac rhythm was regular; the pical impulse was of normal force 1 centimeter beyond the mid-clavicular line i the fifth intercostal space. S_1 was normal nd S_2 was

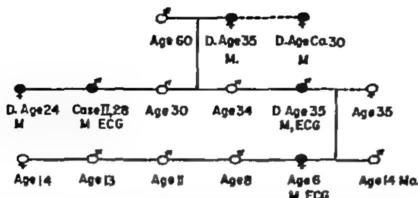


Fig 3 F mily of Case 2. All deceased members were said to have died cardiac deaths, but no diagnoses re recorded other tha *mitral insufficiency in the* brother and suspected entricular septal defect in the sister Electrocardiogram re not ailable in the sister mother and au t. N postmortem examinations were performed. The similarity between the electrocardiograms of Case 2 of h deceased brother and of his iece is striking *M* Heart murmur present *ECG* ECG bnormalities Case 2 or similar to Case 2.

normally spl t with respiration, with slightly accentuated second component. A Grade 2 systolic ejection murm was present along the left ternal border transmitted t the pex and weakly t the base but not t the neck or axilla. A pical diast lic rumble nd opening snap were lso heard. The electrocardiogram is shown in Fig 2 A chest roentgenogr m howed heart t the upper limit of normal ize rounded in contou and suggesti of bi entricular enlargement The aortic rch ppeared t be smaller tha normal. The initial dif ferential diagnosis included mitral tenosis and entricular septal defect Findings obtained by catheterization of the right side of the heart proved t be essentially normal Determinations of blood oxygen nd dye-dilution studies showed no intra cardiac shu t Catheterization of the left entricle showed entricular pressure of 140/0-6 mm. Hg the pressure fell t 90/0 6 the infund bular area, and the aortic pressure was 90-100/60 Mean left atrial pressure was 10. A cineangiogram wa inadequate t delineat the inf ndibular chamber but both coronary arteries ere shown reasonably well. The findings ere those of hypertrophic subaortic stenosis.

This patient mother t, sister nd brother had all died suddenly ith ndiagnosed heart mu murs (see Fig 3). The sister and brother had complained of episodes of tachycardia their systolic murmurs were thought to represent ventricula septal defect nd mitral insufficiency respectively but cardiac catheterization tudies were not made The brother chest films showed left ventricular but not atrial enlargement. This brother 6-year old daughter ha early syst lic murmur along the left sternal border nd be nd his daughter ha electrocardiogram simi lar t those of the patient

Case 3 Thi 40-year-old ma was first admitted t the hospital t the ge of 36 with a newly noted cardiac murmur and poss ble subacute bacterial endocarditis. Vital signs were normal, with blood pressure of 120/75 mm Hg Cardiac rhythm wa regular slight enlargement of the left side of the heart was present P exceeded A Grade 4 rough blowing, medium-pitched systolic m rmur w heard, maximal at the pex with radiation t the posterior axillary line, left sternal border nd aortic rea, but not to the neck. N signs of endocarditis were found, and blood cultures were terile The electrocardiogram thought t be consistent with atrial enlargement and high lateral myocardial infarction (Fig 4). A ectorcardiogram indicated anterolater l myocardial infarction with possible left ventricula hypertrophy but there was no laboratory evidence of acute myocardial damage, nd an exercise tolerance test was normal. Level of serum cholesterol ranged from 292 t 408 mg per cent Cardiac fluoroscopy showed slight left ventricular nd left trial enlargement but no cal cification or dilatation of the aorta. The findings made by catheterization of the right side of the heart were consistent with moderately elevated left entricular end-diastolic pressure Venous pressure nd circulation time were normal. During this period of hospit lization the electrocardiogram *remained stable except for a tra sient complete* right bundle branch block which did not lter the bnormal Q waves in limb nd precordial leads. The discharge diagnosis of rheumatic heart disease with mitral insufficiency was hallenged by some who thought that arteriosclerotic heart disease with myocardial infarction was the more likely diagnosis. After discharge the patient occasionally had pain in the left side of the chest during rest nd on exertion this wa relieved by nitroglycerin and Nardil. H now complains of lightheadedness without frank syncope A phonocardiogram has demonstrated that the murmu is diamond shaped mid-syst lic nd end ith soft second sound. Catheterization of the left side of the heart ha show no pressure gradient across the aortic al and no certain infundibular change but explor tion

for a gradient in the inf ndibular chamber was not specifically undertaken since the possibility of subaortic stenosis was not considered t that time. The contour of the central ortic pulse, however showed a steep initial spike followed by smaller prolonged rise very similar t that seen in Case 1 Moreover the central ortic pulse pressure of the beat following prematur entricular beat was lower than that following normal beats, finding which is considered t be unique to hypertrophic subaortic stenosis.[20] Additional normal tudies ha included coronary angiography left entriculography (no inf ndibular chamber localized no mitral regurgitation), and dye-dilution studies for septal defect. A hest roentgenogram show globular heart with prominence of the left entricle and pulmonary outflow tract There is no evidence of progressive congestive heart failure. The diagnosis is in doubt, but the murmur suggest hyper trophic subaortic stenosis as do the central aortic pulse tracings.

One brother of this patient has Grade 2 systolic murmur along the pper left sternal border which becomes inaudible ith deep inspiration, and n abnormal electrocardiogram consistent with old inferior myocardial infarction, for which there is no history Another brother is said t have had al ular heart disease from childhood A sister electrocardiogram is normal and she has no heart murmur

Case 4 This 19-year-old ma was found t the age of 14 to have had an pical systolic murmur transmitted t the base of the heart and electrocardiogram identical to his present tracing H has been

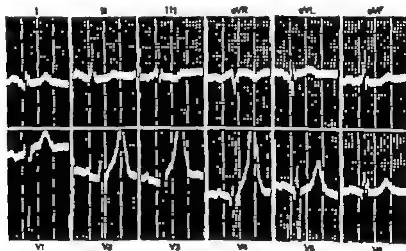
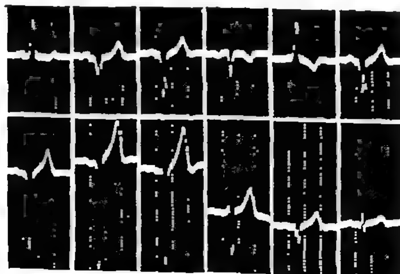


Fig 4 Electrocardiogram of Case 3


Fig 5 Electrocardiogram of Case 4

asymptomatic, with no history of scarlet fever rheumatic fever or familial early heart disease. After he had been hospitalized for meningitis at another hospital we examined him. Vital signs were normal, with a blood pressure of 130/80 mm Hg Cardiac rhythm was regular and the heart was normal except for a Grade 2 harsh murmur which filled the first two thirds of systole maximal along the upper left sternal border with faint transmission to the neck and a Grade 1 diastolic blow also heard along the left sternal border There was no thrill or ejection click The electrocardiogram is shown in Fig 5 A vectorcardiogram showed changes consistent with anterior and inferior myocardial infarction A ballistocardiogram was normal. A chest roentgenogram showed a heart of normal size but with an unusual globular shape, suggestive of biventricular hypertrophy There was no dilatation of the aorta or intracardiac calcification. This patient has refused to undergo cardiac catheterization, but hypertrophic subaortic stenosis is one diagnostic possibility

Neither parent of this patient has cardiac symptoms or signs, and their electrocardiograms are normal but, of 3 siblings 2 have basal systolic murmurs Grade 1 2 which are faintly transmitted to the neck and apex A 22 year-old brother has incomplete right bundle branch block, demonstrated by electrocardiograph with normal but prominent Q waves in Leads V_{5-6} An 8-year-old sister has only the prominent Q waves. The electrocardiogram of the third sibling who has no heart murmur is normal but dissimilar lacking Q waves. All 3 siblings are well.

Discussion

The significant abnormalities in these cases are the deep Q waves and notched QS or W-shaped complexes in limb and/or left precordial leads, together with strongly upright T waves Case 4 exhibits the most diffusely abnormal electrocardiogram with additional QS complexes in Leads V_1 through V_3. These patients have P R intervals which range from 0 12 to 0 20 second without delta waves or QRS prolongation Only Case 3 has shown abrupt transition from one type of depolarization to another and on a single occasion this patient developed transient right bundle branch block during which the abnormal Q waves remained prominent. The S-T and T wave changes which are anticipated with myocardial infarction have never been observed

In order to place these observations in perspective we have reviewed the electrocardiographic findings in 34 reported cases of hypertrophic subaortic stenosis proved at autopsy operation or cardiac catheterization [2-3] Left ventricular hypertrophy is the usual and anticipated finding It appeared in 26 reported cases and in 2 of our proved cases not included in the foregoing case descriptions. One complete and one incomplete left bundle branch block were also noted as well as one complete right bundle branch block. The electrocardiogram of the youngest patient with this disorder a 1 year-old boy showed a short P R interval severe left ventricular hypertrophy and a possible intraventricular conduction delay [13] A recent case report notes the abnormal electrocardiogram of a 30-year-old woman with pectus excavatum and QS waves in Leads V_1 through V_3.[14] There was no history suggestive of coronary artery disease, and the abnormality was unexplained Leads V_1 through V_3 in our Case 4 are similar

Of particular interest are 4 of Braunwald's cases in which the electrocardiograms are characterized as showing anomalous A V excitation [3] The first of these patients had a short P R interval a probable delta wave and the changes of left ventricular hypertrophy There were no abnormal Q waves. The other 3 siblings who ranged in age from 19 to 22 years had abnormal Q waves and W-shaped complexes in a limb lead and the left precordial leads with upright T waves. RSR in Lead aV_R appeared in 2 of the 3 the third was thought to have a QRS deformity related to a prolonged and prominent delta wave best seen in Leads I aV_R and $V_{1,2}$ and resembling complete right bundle branch block. In 2 of these cases, serial electrocardiograms over 8 years showed that the abnormalities were developing with growth they had been less marked in childhood Many other members of this family were said to have heart murmurs and several had died suddenly in childhood or during early adult life. Braunwald comments that "The observation of anomalous atrioventricular excitation in the three siblings . . . supports the concept that, in some instances at least this electrocardiographic finding may be familial " He examined 75 persons related to his patients but found no other cases of hypertrophic subaortic stenosis or anomalous A V excitation Pare and others, however in studying several gen

erations of one family with idiopathic myocardial hypertrophy found at least 3 teen-age family members whose hypertrophy took the form of obstruction to left ventricular outflow and whose electrocardiograms showed abnormal Q waves.[14] Hollman[9] similarly studied 5 members of one family who were suspected clinically of having obstructive cardiomyopathy that involved the left ventricle. 2 relatives had died suddenly and been found at autopsy to have this condition. Hollman found a Q III. This abnormality in 4 of the survivors.

We recognize, therefore that the findings we describe occur in only a minority of patients with hypertrophic subaortic stenosis. The relationship between the electrocardiographic abnormality and anatomic change in this condition remains speculative. There is as yet no single pathologic picture associated with the clinical entity of hypertrophic subaortic stenosis. Brock noted that the clinical signs and symptoms could occur secondary to left ventricular hypertrophy of prolonged hypertension. This group apparently does not exhibit the electrocardiographic changes under discussion.[17] We are concerned more with idiopathic hypertrophy but, even within this group autopsy descriptions vary. Teare's cases were the first in which full pathologic study was made. He consistently noted asymmetrical ventricular hypertrophy with disproportionate involvement of the interventricular septum. Microscopically there was bizarre arrangement of bundles of muscle fibers of varying sizes. Endothelized clefts and connective tissue separated these bundles and extended through the septum. There was no evidence of coronary artery disease, cardiac glycogen storage disease, myocarditis, or subendocardial fibroelastosis. Brent also found predominantly septal hypertrophy with enlargement of individual muscle fibers. He too noted patchy areas of interstitial fibrosis and occasional small areas of replacement fibrosis, especially in the endocardium but not extending deeply into the myocardium and not accompanied by vascular changes. Elastic fibers were not increased. In Bercu's case[3] there was marked symmetrical hypertrophy with normal endocardium save for a 2 by 3 cm. thickened patch along the septal portion of the left ventricular outflow tract and small (2 mm.) focal areas of scarring in the septum and left ventricular muscle with focally narrowed coronary arteries without occlusion. Degenerative changes, inflammatory infiltrate, amyloid and abnormal amounts of fat and glycogen were not seen. Daoud's patient, a child, had generalized muscular hypertrophy without fibrosis, vessel disease, or other abnormality.[18]

From these descriptions it appears possible that patchy myocardial fibrosis and endothelized clefts may alter electrical conduction through the ventricles. In some patients, ventricular hypertrophy and altered conduction may appear earlier and be more severe than in others. Since the ventricular septum is most affected, the earliest electrocardiographic changes may be prominent septal Q waves, which progress to generalized left ventricular hypertrophy and then, in a few individuals, to the abnormalities we describe. Against this explanation, however, is the youth of our patients. Case 4 is known to have had electrocardiographic changes in their present form at the age of 14, and the niece of Case 2 has prominent left precordial Q waves at the age of 6. No patient with the electrocardiographic changes we describe has come to autopsy, and several autopsied cases of hypertrophic subaortic stenosis with Teare's pathologic picture have had only the changes of left ventricular hypertrophy demonstrated on the electrocardiogram.

We conclude only that these electrocardiographic abnormalities have some association, now unexplained, with hypertrophic subaortic stenosis. As Braunwald has shown, other conduction disturbances also occur in this condition, including the ectopic atrioventricular excitation of Wolff-Parkinson and White. Pre-excitation of this type is of course not limited to hypertrophic subaortic stenosis, and it may be that the changes we describe will also be found in other cardiac disorders. One of us (D.L.) reviewed the literature of idiopathic myocardial hypertrophy and observed that, in 3 patients in whom the diagnosis was made by excluding other pathology, the electrocardiograms were

read as showing myocardial infarction[18] as were the electrocardiograms of several of our patients Generalized idiopathic myocardial hypertrophy and hypertrophic subaortic stenosis may however be variants of the same disorder Paré reports finding both conditions in the same family with hereditary myocardial disease[9]

Recognition that the electrocardiographic changes we described need not mean coronary artery disease in a young person may prevent a diagnosis of myocardial infarction and initiate further investigation If hypertrophic subaortic stenosis is found surgical treatment is now available when symptoms warrant it[3,13] In any event the incidence and variations of these changes will be further elucidated

Summary

Electrocardiographic findings simulating myocardial infarction are reported in 4 young persons in whom a diagnosis of hypertrophic subaortic stenosis was proved or considered clinically The pathology of this condition is reviewed Although the electrocardiographic abnormalities may be helpful in making the diagnosis, their association with it remains speculative

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Angina pectoris in father and son

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It is generally accepted that there is a strong familial factor in coronary artery disease and that males overwhelmingly predominate over females until the age of [illegible]0 years is reached. It would not be surprising, therefore, when treating a patient with angina pectoris or coronary thrombosis, to obtain a history that the father had died of the same condition. If a physician practiced long enough, he also would live to actually see and treat both father and son and not have to depend upon family history to show the importance of the hereditary factor in this condition.

During the past four decades I have had the opportunity of seeing a number of individuals with coronary artery disease and then attending the sons of the same patients with a similar disorder. What has been most disturbing is the fact that the children appear to be afflicted with coronary disease at a much earlier age than were their parents. After repeatedly seeing young men with angina pectoris at the age of 40 years or so and then realizing that I had seen their fathers with coronary disease at the age of 60 years or older, I thought that it would be worth while to examine this problem systematically. Are patients developing coronary artery disease at an earlier age than their parents did, and, if so, what is the cause of the acceleration of this atherosclerotic process?

A review was made of all the cases of angina pectoris or coronary thrombosis that I had personally observed in private practice in which both father and son were found to have the same condition (Table I). This includes only those whom I examined myself and those in whom the diagnosis was definite. There were 20 such families and 41 individuals. In one instance there were 2 sons and their father, and there were 2 females in the entire group, one a mother and the other a daughter.† In the other 18 families the patients were all fathers and sons. It must be stated that probably these are not all the instances that I have seen, since I must have overlooked some, especially when married daughters had necessarily changed their names.

The average age at the onset of symptoms of coronary artery disease among the 20 parents was 61.2 years (Table II). For the 21 children it was 48.1 years. This is a difference of 13.1 years. The average age at death of the 14 fathers who had died was [illegible] 7 years, and the average age of the 6 who were still alive was 74.[illegible] years. The age for the entire 20 parents, at last follow-up or at death, was 70.4 years. The final figure for the age at death of the entire 20 will obviously be greater than 70 years, since 6 are still alive. In contrast, the average age at death of the 8 dead sons was 54.8 years. The average age at death of the fathers of 7 of these dead sons (one father was still living) was 67.7 years.

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†In further references, for the sake of simplicity, all cases will be regarded as males.

Table I

Subject	Age when first seen (yr.)	Age at onset of symptom (yr.)	Age at death (yr.)	Age at last follow-up (yr.)
N L	65	65	65	
S L	53	53	53	
D S	68	68	68	
H S	54	51		55
B G	54	52	79	
J G	50	50		61
S S	56	55	70	
W S	47	47	48	
F A	73	69		73
F A J	39	37		46
B K.	49	66		77
S K.	49	49		53
N E.	65	68	83	
C E	38	38	50	
L A	62	62	62	
S A	57	57	73	
H I	75	75		81
E B	55	55		59
A M	65	53	66	
E M	34	33	41	
T L	61	60	66	
N L	49	48		52

This was 13.9 years younger than the age at death of their parents who had already died. The age of the 13 sons who were still alive was 53.2 years and that of all 21 sons was 52.9 years. The age at death may well be greater than the above-mentioned figure of 54.8 years because of the 13 who are still living at an average age of 53.2 years. There were 5 families in which both fathers and sons were still alive. The average age of the fathers was 74.4 years and that of the sons was 48.4 years. It is clear from the foregoing analysis that among the children the evidence of coronary disease started about 13 years earlier than in their parents and that the age at death of those who died was about 13 years younger than that of their parents. Because 13 of the children and only 6 of the parents are still alive the difference in the final average age at death is likely to be somewhat less than the 13 years mentioned above. Although the number of cases is obviously small the difference of 13 years seems to be too great to be insignificant.

The first question that arises is whether the statistical data are fallacious. One factor that may have a bearing on these figures is that all the children of the parents have not been examined or have not yet lived their entire span of life. As years go on may not some of the sons who are alive and well develop coronary artery disease later in life? This could increase the average age of the second generation above the figures that have been found in this study. Only time can answer this question. It will be difficult for one physician to live long enough to accumulate

Table I—Cont'd

Subject	Age when first seen (yr.)	Age at onset of symptom (yr.)	Age at death (yr.)	Age at last follow-up (yr.)
H F	43	49	[illegible]	
N F	38	38		47
L T	53	52		71
S T	41	41	41	
H M	40	62		76
F M	45	45		50
L C	61	65		65
F C.	31	31		37
W R.	61	55	61	
J R.	49	49		51
H W	58	58	77	
J W	49	60		62
S C.	61	65	[illegible]	
J C	31	64	64	
I S.	58	55	60	
A.S.	45	45	68	
L.B	69	68	84	
D B	36	51		56
H B	57	65		65

data from his own personal experience and to see parents as well as all their children until their deaths.

If we assume that, when all the children are observed until their death, the average age at the time coronary symptoms appear is still definitely lower than that of their parents, what may the factors be that accelerated the development of this disease? The average difference in age between fathers and sons was 26.5 years. What changes in environment may have taken place during that quarter of a century? One wonders whether a change in diet occurred or whether an increase in the tension of modern living, or some more specific cause, is behind all this.

There is one genetic aspect of the problem that may be playing a role. In a study of this type we know that the son had at least one parent with a history of coronary disease. The other parent may also have had this same stigma. In this analysis, the status of the parents of the fathers is not known. It is extremely unlikely that coronary disease was present in all the grandfathers as it was present in all the fathers. In other words, we know that the genetic factor was much more prevalent in the background of the sons than of their fathers. When it is appreciated that one of the known factors in coronary disease is heredity, it would not be surprising if sons of parents with known coronary disease would be more "severely" afflicted with the same disease than were their parents, for the latter may not have had any such tendency. Furthermore, if the genetic tendency is greater, the disease in the offspring may not only be more frequent, but may become manifest at an earlier age.

There is an average difference of 26.5 years between the ages of the fathers and the sons. Although it would be expected that the fathers would manifest the first evidence of coronary disease before their sons despite the fact that the condition was appearing at an earlier age in the children, there were 4 instances in which the sons were afflicted before their fathers. The average interval of time between the onset of symptoms in all the fathers and sons was 13.0 years. The average interval in 17 instances in which the sons followed the fathers was 16.9 years, and when the sons preceded the fathers, the average interval was 3.3 years.

Not only did this condition seem to come earlier in life in the second generation, but it also appeared to be more severe. The duration of life from the onset of first symptoms to death in all 14 parents who had died was 9.2 years, whereas the cor-

Table II

Average age at onset—Fathers (20)	61.2 yr
Average age at onset—Sons (21)	48.1
Average age at death—Fathers (14)	68.7
Average age at death—Sons (8)	54.8
Average age at death—Fathers (7) with living sons	69.7
Average age at death—Fathers (7) with dead sons	67.7
Average age of living sons (8) of dead fathers	55.9
Average age of living son (5) with living fathers	49.0
Average age of fathers (5) with living sons	74.4
Average age of dead fathers at onset (14)	59.5
Duration of symptoms in dead fathers (14)	9.2
Average age of dead sons at onset (8)	47.3
Duration of symptoms in dead sons (8)	7.5
Average age of all fathers at death or last follow-up (20)	70.4
Average age of all sons at death or last follow-up (21)	54.4
Average age of living fathers (6)	74.0
Average age of living sons (13)	53.2
Average interval between onset in fathers and sons (21)	13.0
Average interval—father before son (17)	16.9
Average interval—father after son (4)	−3.3
Average difference of age between fathers and sons (21)	26.5

responding figure for the 8 dead sons was 7.5 years. This difference is not great, but one would have expected opposite findings. The treatment of coronary disease is thought to have improved during the past 30 years. This certainly is true of coronary thrombosis. The better use of oxygen, anticoagulants, pressor drugs, the more effective control of arrhythmias, having patients in a chair during the early days of the attack, and more accurate and earlier diagnosis must have decreased the immediate mortality of the acute attacks of myocardial infarction. Furthermore, one might suspect that in earlier years the history of the onset of the very first anginal symptoms might not have been obtained so accurately as in more recent years. Both of these factors ought to have indicated a longer survival period after the onset of the disease in the sons than in the fathers. Despite this, the sons have not lived quite so long as the fathers. The possible conclusions that can be drawn are that these data are incorrect, that our therapy has not been improving significantly, or that the disease itself is becoming more severe. The problem is sufficiently important to deserve further investigation. More prolonged study and a larger number of cases will be needed before a final and convincing answer can be obtained.

Summary

Angina pectoris or coronary thrombosis were personally observed in 20 fathers and 21 sons. It was found that the first evidence of coronary disease in the sons appeared at an age 13.1 years younger (48.1 years) than that of the fathers (61.2 years). The average age at death of 8 sons was 54.8 years and that of 14 fathers was 68.7 years, i.e., a difference of 13.9 years. The duration of coronary symptoms in the dead sons was 7.5 years and that in the dead fathers was 9.2 years. The possibility of statistical errors in this type of study was discussed. The evidence suggests that some factors are at work which cause coronary artery disease to appear at a younger age and run a more severe course in the present than in the previous generation.

Reflex vasomotor activity during unilateral occlusion of the pulmonary artery

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It has been stated for many years that the main branches of the pulmonary artery have no pressure receptors,[4] although in some perfusion experiments the main trunk appeared to respond to an increase in flow by producing bradycardia. The mechanism was claimed to be reflex, and an increase in the heart rate was seen after vagotomy.

Recently, two groups of investigators described a certain number of baroreceptors located in the trunk and main branches of the pulmonary artery, with electrophysiologic evidence that the impulses ran through the vagus nerve. It has also been pointed out that the occlusion of one branch of the pulmonary artery brought about bronchoconstriction in the homolateral lung.

All these facts call attention to the importance of a rather unknown reflexogenic area in the pulmonary vascular bed.

Controversy has arisen concerning the behavior of the pulmonary arterial pressure after the occlusion of one branch of the pulmonary artery, depending on whether the occlusion was performed by clamping the vessel or by means of an inflatable balloon.[12] Inasmuch as the pulmonary vascular bed did not change with unilateral occlusion of the pulmonary artery,[9,12] it is necessary to explain the discrepancy in the results of these two procedures.

This work was planned to study the vasomotor activity of the lungs after occlusion of one branch of the pulmonary artery, and the implications of the autonomic nervous system, the release of catecholamines added to sympathetic blockade, and the influence of pretreatment with reserpine.

Methods

Mongrel dogs were anesthetized with pentobarbital (35 mg. per kilogram intravenously). The following procedures were routinely performed on all animals: (a) cannulation of the trachea for either spontaneous breathing or artificial positive pressure respiration, (b) catheterization of the pulmonary artery to allow measurements of pressure and occlusion of one branch of the vessel with an inflatable balloon (Fig. 1), (c) insertion of a catheter into the femoral artery.

Cardiac output was estimated by the

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Table I Results obtained in dogs by means of blocking agents and surgical denervation

Experiment number	Weight of dog (Kg)	Situation Drug (mg/Kg)	Systemic BP (mm Hg)	Pulmonary arterial BP			Cardiac output (L/min)
				mm. Hg	Δ		
					Systolic	Diastolic	
1	21	Control	130/90	24/7			3.50
		Occlusion	130/90	30/10	+25	+43	3.80
		C 15 + atropine 0.3	0 50	15/4			0.98
		Occlusion	70 50	19/6	+26	+50	1.10
	30	Control	140 115	27/6			1.32
		Occlusion	140/115	36/10	+33	+66	1.75
		C 15 + atropine 0.3	55/40	1 /5			0.62
		Occlusion	55 40	25/9	+47	+80	0.75
3	14	Control	120 5	32/11			2.44
		Occlusion	120/75	45/13	+40	+18	2.33
		Guanethidine 10	160/100	40/18			4.02
		Occlusion	160/100	55/25	+38	+40	2.15
4	12	Control	133/96	30/9			1.52
		Occlusion	135/96	42 12	+40	+33	1.52
		Guanethidine 10	180/129	30 18			1.36
		Occlusion	180 130	45/23	+30	+28	——
5	6	Control	120/90	22/8			3.75
		Occlusion	120/90	30/9	+36	+13	3.90
		Guanethidine 10	235 162	37/11			5.03
		Occlusion	230/160	46/13	+24	+18	7.90
6	23	Control	185 125	30/9			3.21
		Occlusion	185/125	38/12	+27	+83	3.31
		Guanethidine 10	240 165	35/17			3.20
		Occlusion	240 165	47/22	+34	+30	3.20
7	21	Control sympathectomy	150/72	30/11			2.47
		Occlusion	150/75	38/14	+27	+27	2.53
		Vagotomy	150/70	30/12			2.70
		Occlusion	150/ 5	38/14	+27	+47	2.80
8	27	Control sympathectomy	183/124	30/13			3.98
		Occlusion	183/124	43/15	+43	+15	3.90
		Vagotomy	181/122	30/13			2.60
		Occlusion	181/122	40/15	+34	+15	2.75

direct Fick method. Pulmonary and systemic blood pressures were recorded by Statham transducers on a Sanborn Twin Viso. Samples of blood were analyzed by the manometric method of Van Slyke and expired air was analyzed in a Scholander microanalyzer.

Dogs without treatment. In every experiment, two control determinations of cardiac output and pulmonary arterial and systemic blood pressures were made one in the resting condition and the other after 10 minutes of occlusion of one branch of the pulmonary artery. In addition another pair of determinations was made after one of the following procedures (1) intravenous injection of hexamethonium bromide (15 mg/Kg) and atropine sulfate (0.3 mg/Kg) in 2 dogs (2) intravenous injection of guanethidine (10 mg/Kg) in

Table II Results obtained in open-chest preparations and local anesthesia

Experiment number	Weight of dog (Kg.)	Situation Drug (mg./Kg.)	Systemic BP (mm. Hg)	Pulmonary arterial BP mm. Hg	Pulmonary arterial BP Δ% Systolic	Pulmonary arterial BP Δ% Diastolic	Cardiac output (L./min.)
9	18	Control	140/100	22/12			0.64
		Occlusion	140/100	30/13	+36	+8	0.78
		Local anesthesia	120/75	25/15			0.40
		Occlusion	120/75	25/15	0	0	0.35
10.	21	Control	130/90	32/12			2.45
		Occlusion	130/90	39/14	+22	+17	2.36
		Local anesthesia	130/90	32/12			1.50
		Occlusion	130/90	32/12	0	0	1.50
11	27	Control	140/120	32/14			2.30
		Occlusion	140/120	43/18	+34	+28	2.50
		Local anesthesia	140/120	22/12			1.73
		Occlusion	140/120	22/12	0	0	1.65
12.	25	Control	110/85	30/16			1.56
		Occlusion	110/85	38/22	+27	+36	1.70
		Local anesthesia	115/95	23/15			2.00
		Occlusion	115/95	23/15	0	0	2.20
13.	19	Control	180/120	31/21			0.71
		Occlusion	180/120	39/29	+25	+37	0.75
		Occlusion + saline infiltration	180/120	39/29	+25	+37	—
		Local anesthesia	180/120	27/20			0.79
		Occlusion	180/120	27/20	0	0	0.74
14.	11	Control	120/95	22/10			0.95
		Occlusion	120/95	29/13	+32	+30	0.99
		Occlusion + saline infiltration	120/95	29/13	+32	+30	—
		Local anesthesia + occlusion	120/95	22/10			0.89

Table III Reserpinised dog (0.75 mg./Kg.) 24 hours previously

Experiment number	Weight of dog (Kg.)	Situation	Pulmonary arterial BP mm. Hg	Pulmonary arterial BP Δ% Systolic	Pulmonary arterial BP Δ% Diastolic
15.	18	Control	24/7		
		Occlusion	30/10	+25	+43
16.	20	Control	30/9		
		Occlusion	42/12	+40	+33
17	19	Control	22/8		
		Occlusion	30/9	+36	+13

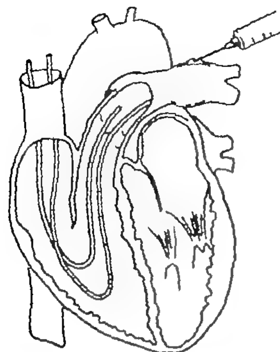


Fig 1 Both the pressure-recording and balloon catheters are located in the pulmonary artery The syringe and needle indicat the he t which local anesthetic is infiltrated

4 dogs (3) denervation of the heart and lungs, accomplished by combined bilateral excision of the thoracic sympathetic ganglia (T_1-T) and cervic l vagotomy in 2 dogs and (4) infiltration of the pulmonary artery with 2 per cent Xylocaine at the site to be occluded performed through a thoracotom in 6 dogs (see Fig 1)

In the first three groups of dogs the determinations were carried out with the chest closed and the animals breathing spontaneously the catheters were guided under fluoroscopic control In the fourth group the dogs were subjected to thoracotomy and were under artificial respiration during the entire experiment i.e control and postinfiltration determinations.

Reserpinized dogs Reserpine (0 .5 mg Kg) was administrated intraperitoneally to each of 3 dogs 24 hours before they were tested with the pulmonary artery occluded by means of a balloon At the time of study a smaller quantity of pentobarbital than that used in the preceding group of dogs was injected intravenously (approximately 20 mg /Kg) in order to prevent the animal from dying

Results

A total of 61 determinations in 17 dogs was carried out (Tables I II and III)

Pulmonary arterial pressure After occlusion of one branch of the pulmonary artery there was an immediate rise in pulmonary arterial pressure this averaged 9 6 mm Hg systolic and 2 6 mm. Hg diastolic in the closed-chest preparations The corresponding values in open-chest animals were 8 2 and 4 0 mm Hg respectively

The mean increase for all the experiments was +32 per cent (22 to 43 per cent) for systolic pressure and +29 per cent (8 to 66 per cent) for diastolic pressure. The percentage increase was maintained with slight modifications, after blockade of the sympathetic and parasympathetic nervous pathways, surgical denervation or pretreatment with reserpine. On the contrary local anesthesia completely abolished the response i.e there was no change in pulmonary arterial pressure after occlusion (see Fig 3) The difference in behavior is significant when one takes into consideration the control observations in each individual dog and the fact that infiltration of the arterial wall with saline (Experiments

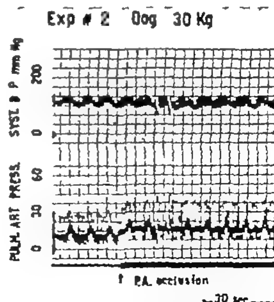


Fig 2 Typical response to occlusion of one branch of the pulmonary rtery There is no cha ge in sy temic blood pressure but rise in systolic nd dia tolic pressures in the pulmonary rtery

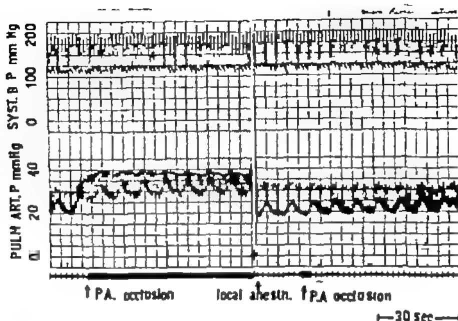


Fig 3 The usual response with increase in pulmonary arterial pressure is blocked by 7 c of 2 per cent Xylocaine. Note that there is no modification systemic blood pressure

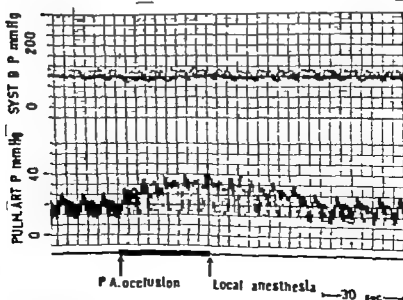


Fig 4 The pressure which rises initially shows drop after local anesthetic is infiltrated into the wall of branch of the pulmonary artery The balloon remained inflated during the recording of the tracing

13 and 14 Table II) failed to prevent the increase in pulmonary arterial pressure Furthermore, in Experiment 14 (Fig 4) the pressure which had risen initially with inflation of the balloon reverted to previous levels after the infiltration of Xylocaine

This procedure also caused a decrease in basal pulmonary arterial pressure in 3 of 6 dogs, a slight increase in 1 and no modification in the other 2.

Systemic arterial pressure In these experiments the occlusion of one branch of the pulmonary artery did not bring about any change in the systemic pressure although in some dogs extreme variations in the values, in comparison with the control values were observed after the administration of blocking agents.

Cardiac output Measurements of cardiac output are known to show great variation on serial determinations during pentobarbital anesthesia but the results in each pair of observations, i e control and occlusion showed only slight modifications. Experiments 3 and 5 (injection of guanethidine) were exceptions to this behavior

Discussion

Many papers [11-13] have categorically denied the existence of receptors in the branches of the pulmonary artery beyond the bifurcation of the main trunk. This conclusion was based on the absence of changes in cardiac rhythm output, and systemic vascular resistance with moderate variations in pulmonary blood pressure during occlusion of one branch with a balloon or an increase in the perfusion flow Furthermore, in some experiments or during pneumonectomy the pulmonary arterial pressure failed to rise when one main branch was tightened or clamped On the contrary the occlusion of one branch of the pulmonary artery by inflation of a balloon constantly brought about an increase in pressure which varied between 20 and 33 per cent of control values. [13]

It must be pointed out that clamping is more traumatic since it necessitates a thoracotomy and dissection of the vessel to be occluded whereas the balloon at times is inadvertently overinflated and provokes partial interruption of flow through the main trunk of the pulmonary artery

The results reported herein allow certain facts to be established

1 The possibility of reducing the rise in pulmonary arterial pressure after occlusion of one main branch of the pulmonary artery indicates that some tone persisted in the patent pulmonary vessels after this latter procedure.

Previous reports of Brofman[14] and Denolin [9] pointed out that in man this initially increased pressure reverted to control values after several minutes of inhalation of oxygen Therefore, the decrease in resistance to the flow of blood through the unoccluded lung is accomplished by means of a vasodilatation or opening of new channels, or both mechanisms but the vessels tone is not abolished

2. The trigger zone of this vasomotor activity is the wall of the artery itself stretched by the balloon since neither pharmacologic blockade of the autonomic nervous system (atropine plus hexamethonium guanethidine) nor complete denervation prevented the rise in pressure. On the other hand in Experiment 14 there was a typical blockade with Xylocaine while the balloon was inflated and the usual elevation in pressure was elicited only after the effect of the drug had passed

It is suggested that the response of pressure to occlusion is not dependent on flow through the unoccluded lung since almost the same percentage increase was obtained in spite of great modification of cardiac output in some dogs. Conversely experiments in which the arterial wall was stretched without interruption of flow also succeeded in obtaining the increase in pressure reported above. [7] Hence, neither the duplication of blood flow through one lung nor complete cessation of it in the other seems to be necessary for producing this event

3 The reflex is pulmo-pulmonary in nature because it does not depend on the integrity of the nervous system but on the sensitivity of the arterial wall. It acts directly on the pulmonary vasculature with no effect on cardiac activity or on the systemic vessels. This type of response appears to be similar to that described for the embolization of a perfused lobe which produces an increase in pressure on the other pulmonary vessels supplied with

blood from the animal's own heart.[18] Another example of the intrinsic vasomotor activity of the lesser circulation was recently reported in a heart-lung preparation in which the increase in pulmonary arterial pressure reduced the flow through the physiologic pulmonary-to-bronchial venous shunt.[19]

4. *The reactivity of the pulmonary vessels,* at least in the case of this particular reflex, is not related to their catecholamine content, since the reaction was essentially the same in the reserpinized dogs and in the animals without treatment.

In a review article Donnet and Ardisson[20] anticipated that the occlusion of one branch of the pulmonary artery would produce general hypertension with vasoconstriction, and it was not abolished by denervation but by local anesthesia of the vessel at the site to be clamped. The authors concluded that it was a nociceptive reflex elicited by the traumatic maneuver of instrument compression.

The existence of baroreceptors in the branches of the pulmonary artery has been proved in cats and dogs, with evidence that the impulses follow the vagal route. The significance of these receptors and their role in the regulation of the pulmonary vascular circuit remains obscure. However, the maintenance of vascular tone during the occlusion of one branch of the pulmonary artery cannot be ascribed to their activity, since vagotomy did not abolish the rise in pulmonary blood pressure.

Most of the apparently *conflicting* results are due to different techniques: perfusion experiments with the inevitable maneuvers of dissection, cannulation of vessels, and the use of pumps; clamping of the arteries that destroys to an unpredictable extent the adventitia and surrounding tissues. On the other hand, the inflation of a balloon until the pulmonary artery is completely occluded is probably accomplished with levels of pressure much greater than those within the physiologic range.

All these facts point to shortcomings in the interpretation and evaluation of reflexogenic areas in the pulmonary circulation. Furthermore, extension of these findings to clinical conditions, such as embolism of the lungs or physiologic exercise, is extremely hazardous.

Summary

In anesthetized dogs, occlusion of one branch of the pulmonary artery by means of a catheter with an inflatable balloon elicited an increase in pulmonary arterial blood pressure, with an average of +32 per cent for the systolic control level and +29 per cent for the diastolic. This phenomenon was not abolished by blocking agents (hexamethonium, atropine, guanethidine), surgical sympathectomy, and vagotomy, or pretreatment with reserpine.

Infiltration of the adventitia of the vessel with Xylocaine at the exact site to be occluded completely blocked the response. In one dog this procedure caused the pulmonary blood pressure, which had risen initially, to revert to control values while the balloon was still inflated.

It is concluded that stretch receptors are responsible for this pulmo-pulmonary reflex action that maintains vasomotor tone activity in the patent pulmonary vessels.

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Changes in serum lipoproteins after a large fat meal in normal individuals and in patients with ischemic heart disease

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Epidemiologic evidence has been accumulated which suggests a relationship between diets high in saturated fat, elevated serum lipids, and ischemic heart disease. Several recent reports have shifted emphasis to triglyceride as the lipid fraction most clearly implicated in the pathogenesis of atherosclerotic disease.[1] Since dietary fat is a major source of circulating triglyceride, it seemed of value to devise a fat loading test analogous to the glucose tolerance test. A fat tolerance test would be expected to stress the capability of the individual to bind the lipid to protein for transport and to remove subsequently the lipid from circulation for storage or oxidation. Several earlier studies[2-4] have indicated that patients with heart disease have an increased and persistent serum lactescence and turbidity as compared to normal subjects. These studies were semiquantitative and afforded no information related to specific features of lipid transport after the ingestion of fat. More recently, radioactive triolein has been utilized as a test meal with a finding of differences in normal and atherosclerotic patients.

Analysis of serum beta lipoproteins by ultracentrifugation affords a reliable and quantitative means of measuring changes in lipid transport after the ingestion of fat. Earlier studies in our laboratory using this test have revealed marked individual differences. The present study expands our experience to an older normal population and to a group of patients with ischemic heart disease. Differences in response to a large fat meal were noted in these groups and offer further support for the concept that basic metabolic differences may be present in patients with atherosclerotic disease.

Methods and materials

A total of 53 tests were performed on 50 male subjects who ranged in age from 17 to 68 years. A history, physical examination, electrocardiogram, and ballistocardiogram were obtained on each subject. The subjects were divided into three groups: (1) young clinically normal subjects, 17 to 30 years of age, who were selected from the laboratory staff; (2) older clinically normal subjects, 31 to 60 years of age, who were working at the Naval Air Station; and (3) patients who had ischemic heart disease that was substantiated by clinical history and electrocardiographic findings. The older normal subjects were

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Table I. Serum lipoproteins in normal subjects 19 to 30 years of age prior to and after ingestion of 120 Gm. of fat

Subject	Age (yr.)	Fasting lipoproteins SF 0-12	Fasting lipoproteins SF 12-20	Fasting lipoproteins SF 20-100	Fasting lipoproteins SF 100-400	Fast. mg. cholesterol (mg. %)	Increase with fat load mg. (mg. %) SF 20-100	Increase with fat load mg. (mg. %) SF 100-400	Test meal eq. valent to 120 Gm. of fat
L T	22	415	50	90	16		34	50	IC
W O C	28	360	18	65	5	182	30	30	WC
R D	30	318	22	82	8		40	22	IC
W H	26	318	20	55	0	152	25	20	WC
R T	25	360	10	0	0		60	19	IC
D B	23	760	35	15	0		30	4	IC
G A	17	230	22	70	5	165	20	5	IC
M S	21	480	45	10	[illegible]	271	26	2	IC
R G	19	335	25	115	55	205	15	25	IC
A L	22	260	10	3	0		[illegible]	50	IC
R McC	21	311	32	106	32	198	18	68	IC
M C	20	606	77	113	77	330	45	72	IC
T G	30	465	50	105	35	262	60	130	IC
R I	23	347	30	125	33	223	30	17	IC
C B	27	465	60	90	40		18	15	IC
T D	21	280	18	64	8	175	22	18	IC
J D	21	280	17	[illegible]	7	167	23	15	IC
J M C	19	333	39	68	6		30	14	IC
R P	24	262	15	8	0		57	8	IC
J G	30	465	51	115	35	262	61	129	IC
W B	20	286	50	124	24		15	17	IC
L Z	18	445	20	100	15	261	85	60	WC
L Z		435	35	105	28		65	85	IC
F W	18	393	30	90	22		33	30	WC
F W		393	32	100	15		13	50	IC
R. D W	19	450	30	100	5		5	42	WC
R D W		480	38	118	18		11	20	IC
M	22 17	391 7	32 6	77 8	18 9	219 [illegible]	35 5	37 8	
S D	±3 9	±113 3	±13 9	±38 [illegible]	±19 8	±51 5	±21 5	±33 8	

IC Test meal of ice cream equivalent 20 Gm. of fat. WC Test meal of whipping cream equivalent [illegible] 120 Gm. of fat

grouped for direct comparison with the patients who had coronary heart disease in order to obviate the influence of age and of difference in test meal. All subjects were ambulatory and on an unrestricted diet prior to the test with the exception of two (D M and R M). The subjects were studied after an overnight fast. During the 12 hour experimental test period only fluids and a single nonfat meal were permitted. They were allowed to continue normal activity which was largely sedentary. The patients with coronary heart disease were tested 6 months or more after infarction and all had resumed at least moderate activity.

The test meal consisted of 120 Gm. of butterfat in the form of whipping cream with 5 Gm. of sucrose and vanilla flavoring. Initially the test meal was composed of a quart of high butterfat ice cream that contained 120 Gm. of fat. This was subsequently changed to whipping cream in order to provide a uniform and unadulterated source of fat. Comparison of the two meals on several individuals revealed no important discrepancies (Table I). Whipping cream was used exclusively as the test meal in the two groups of older patients compared directly (Groups II and III).

Samples of blood were drawn fasting at 3 hours, at 5 hours and at 12 hours after

Table II Serum lipoproteins in normal subjects 31 to 69 years of age prior to and after ingestion of 120 Gm of fat

Subject	Age (yr)	Fasting lipoproteins				Fasting cholesterol (mg %)	Increase with fat load mg (mg %)		Area (increase × time elevated) sq mm.	
		SF 0-12	SF 12-20	SF 20-100	SF 100-400		SF 20-100	SF 100-400	SF 20-100	SF 100-400
R. M	37	400	20	75	10	160	14	28	23	28
C P	39	430	50	105	20		30	18	37	21
J D	29	525	55	5	10		70	15	64	11
W H	48	400	30	90	5		25	24	15	35
I J	42	510	35	240	30		12	40	8	38
N K	47	403	34	14	0		41	25	22	15
T W	44	450	60	100	10		52	20	65	25
D M	34	260	60	55	15	179	25	7	30	9
D B	48	320	35	75	5	262	47	30	59	47
J P	32	390	70	0	0		35	10	25	12
W C	69	470	38	100	28	212	6	18	10	18
P M	39	482	98	150	34	*194	44	83	30	122
C. M	43	335	40	12	0		65	20	90	28
I Y	39	500	45	105	30	260	45	67	65	95
Mean	44 3	419 6	45 7	80 4	14 1	227 8	36 6	28 9	39 5	37 6
S.D	±8 4	±74 5	±19 4	±62 3	±12 6	±48 0	±18 2	±20 6	±24 0	±32 7

*On low-fat diet.

Table III Serum lipoproteins in patients with proved ischemic heart disease prior to and after ingestion of 120 Gm of fat

Subject	Age (yr)	Fasting lipoproteins				Fasting cholesterol (mg %)	Increase mg with fat loading (mg %)		Area (increase × time elevated) sq mm	
		SF 0-12	SF 12-20	SF 20-100	SF 100-400		SF 20-100	SF 100-400	SF 20-100	SF 100-400
H H	54	520	60	115	60	268	52	118	55	155
G H*	53	496	59	162	68	312	17	58	14	70
C. H*	55	522	60	150	50	349	53	64	40	67
J C.	47	558	51	198	85	252	43	40	60	60
S C.	45	515	89	308	51	307	90	55	38	60
J R	49	660	65	100	20	261	13	88	11	80
R C.	[illegible]	605	30	70	5	263	28	23	34	30
C C	51	385	50	30	0	212	17	28	9	26
R. M**	39	460	80	240	80	225	35	10	35	10
N B*	57	510	75	105	20	1	62	61	85	100
D B*	53	485	74	86	18	260	57	52	80	78
E. S	46	490	89	207	107	295	[illegible]	92	75	125
Mean	50 1	515 5	66 8	147 6	47 0	27 9	40 5	54 7	44 7	71 8
S D	±4 8	±65 6	±13 7	±76 0	±33 0	±36 3	±16 6	±28 3	±25 4	±39 4

*Brothers.
**On low-fat diet

ingestion of the fat. Serum lipoprotein fractions Sf 0-12, Sf 12-20, Sf 20-100, and Sf 100-400 were determined at The Institute of Medical Physics, Belmont, California, according to the modified method of standard ultracentrifugation described by Gofman and associates.[3] Serum cholesterol was determined on these samples by the method of Kingsley and Schaffert. When it became apparent that the serum cholesterol varied little with the ingestion of fat, this determination was made only at random on normal subjects but continued on those with coronary disease. No subject had diarrhea during the test period, and the patients with angina pectoris reported no postprandial angina. The results of ballistocardiograms obtained during lipemia have been reported previously. The changes in lipoprotein fractions were plotted for each subject. The lipid elevation was determined by measuring with an integrating planimeter the shaded area in Fig. 1.

Results

Representative curves after injection of the test fat meal are presented in *A* and *B* of Fig. 1, which depict the changes in the fractions of serum lipoprotein. The Sf 100-400 and 20-100 fractions demonstrated the greatest change after the ingestion of fat. These low-density fractions are composed almost entirely of triglyceride bound to β-lipoprotein.[12] Fig. 1,*A* is the graph of findings in a 39-year-old clinically normal subject and demonstrates the phase of alimentary hyperlipemia marked by a rise in the triglyceride-containing Sf 100-400 and Sf 20-100 fractions to a peak at 3 to 5 hours and a return to fasting levels in 8 hours. The serum cholesterol and the Sf 0-12 and Sf 12-20 fractions, which contain primarily phospholipid and cholesterol, did not change significantly. The graph of a patient with proved coronary artery disease is presented in Fig. 1,*B*. The same pattern after fat loading is noted, but the elevations of Sf 20-100 and Sf 100-400 fractions are greater and remain elevated over a longer period. The shaded areas under the curves represent the areas measured with an integrating planimeter and represent a measure of the elevation-time product. The results for young normal subjects, older normal subjects, and patients with coronary artery disease are presented in Tables I, II, and III, respectively.

The marked individual variation in the young normal men may readily be appreciated as well as the overlap in response in the normal and patient groups. Reproducibility of lipemic changes in the same subjects with alternation of test meals (each containing 120 Gm. of fat) is demonstrated also. Although the mean elevation of Sf 100-400 is slightly greater in the patients with heart disease (Table III) than in the older normal subjects (Table II), these changes proved to be at the boundary of statistical significance with respect to maximal increase ($p < .02$) and the calculated area ($p < .05$). There were no significant differences between the groups in elevation of the Sf 20-100 fraction. Although not listed in the table, the Gofman atherogenic index* increased up to 50 points after the fat meal, and this indicates the necessity for obtaining fasting blood for this determination.

In spite of the limited number of observations, several other interesting relationships were apparent. Significant differences were present between the patients with heart disease and both groups of normal subjects with respect to fasting levels of Sf 20-100 and Sf 100-400. This finding is in concert with the demonstration of significantly higher levels of fasting serum triglyceride in patients with proved myocardial infarction.[8,9] A correlation was present between fasting cholesterol levels and elevations of Sf 100-400 after the ingestion of fat in each of the three groups ($r = +0.48$ to $+0.79$). There was also a relationship between the fasting Sf 100-400 level and the elevation of this fraction as evidenced by correlations of +0.43, +0.58, and +0.33 in Groups I, II, and III, respectively. Two sets of brothers with ischemic heart disease were studied (G.H., C.H., and N.B., D.B. in Table III). There was a similarity between brothers in both the fasting lipoproteins and the responses after the fat meal. Of additional interest is the observation that the two subjects (D.M. and R.M.) on low fat diets had the

*Atherogenic index = 1 (Sf 0-12) + 0.17 (Sf 12-400).

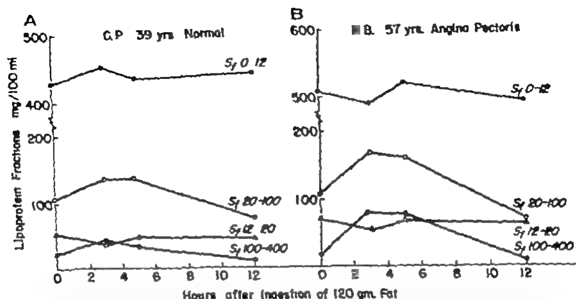


Fig. 1. Changes in serum lipoprotein fractions after ingestion of 120 Gm. of butterfat. *A*, Clinically normal individual. *B*, Patient with myocardial infarction. The shaded area represents the time-elevation of the triglyceride-containing Sf 20-100 and Sf 100-400 fractions. The increase in these fractions was more marked in the patient with ischemic heart disease. No significant changes were apparent in the Sf 0-12 and Sf 12-20 fractions.

least elevation within their respective groups. Fat restriction had been instituted in these individuals because of elevated cholesterol and had resulted in a reduction of serum lipids.

Discussion

Alimentary hyperlipemia after ingestion of a large fat meal was present in each individual but the degree varied with age and clinical status. Although these studies should be considered as exploratory rather than conclusive, a definite and significant trend in the response to a fat load was evident in the groups studied. Patients with atherosclerotic disease and normal individuals with high cholesterol values demonstrated a greater and more persistent elevation of the triglyceride-containing lipoprotein fractions than a comparable group of normal individuals. In addition, fasting levels of these lipoprotein fractions were elevated in patients with ischemic heart disease. The results obtained by direct measurement of the lipoproteins are in agreement with the observations of other investigators utilizing a less direct approach. Early observations by Moreton and others[-4] indicated that patients with heart disease exhibited greater lactescence and turbidity of the serum and an increase in the β-lipoprotein fractions after a high fat meal. Likoff and associates have demonstrated that atherosclerotic patients and healthy individuals with hypercholesterolemia have a different pattern of absorption and removal of radioactive triolein. It is apparent from the present studies that there is a significant overlap in response to fat ingestion between the normal groups and the group with proved coronary artery disease. This overlap would be anticipated if metabolic differences were of importance in the pathogenesis of atherosclerosis which is a common disease. Within a healthy young population many members would be expected to express a decrease in the ability to handle a fat load. In older groups the difference in fat tolerance between normal and abnormal groups would be more pronounced as these differences become associated with clinically apparent disease. Our results are in keeping with this general concept. Some of the overlap of the "normal" groups was due to individuals with elevated fasting lipids, either cholesterol or low-density lipoproteins. Since these

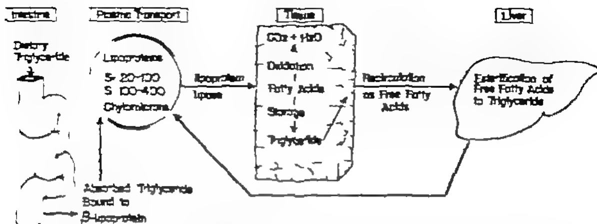


Fig. 4. A simplified scheme of triglyceride transport and metabolism. As indicated in the diagram, elevations of the low-density lipoprotein fractions (Sf 20-100 and Sf 100-400) in plasma could result from decreased removal by lipoprotein lipase, altered mobilization and recirculation as free fatty acids, or changes in the hepatic esterification of fatty acids to triglyceride. An alteration in the transport protein moiety might also result in altered binding of the triglyceride to the lipoprotein.

studies are related to the development of atherosclerotic disease, it is apparent that these individuals are "normal" only with respect to not having apparent disease. Thus, the present study and those previously cited indicate that patients with atherosclerosis have a decrease in their ability to handle lipid. This defect has been further localized to the low-density lipoprotein fraction, and the metabolism of this fraction deserves consideration.

The fate of the lipid contained in the elevated lipoprotein fractions is a complex series of events, many of which are interrelated (See Fig. 4). After absorption from the gastrointestinal tract, triglyceride is transported in the plasma bound to β-lipoprotein; this moiety constitutes the low-density Sf 20-100 and Sf 100-400 fractions measured in this study. At the tissue sites the lipid-protein complex is broken, and, in turn, the fatty acids are split from the triglyceride. This cleavage is probably the result of an enzyme, lipoprotein lipase. The lipolytic activity in the serum due to this enzyme is increased after a fat meal or the administration of heparin. The fatty acids which have been released may be utilized for oxidation, storage, or return to the circulation as albumin-bound free fatty acids. Completion of this cyclic process may occur with esterification of these same fatty acids (or tissue fatty acids in equilibrium with them) into triglyceride and low-density lipoprotein.[14-21] Alterations in any part of this complex mechanism would result in differences in fasting and postprandial levels of lipoproteins. The similarity of response within the atherosclerotic group does not mean that the same etiological mechanism is operative in each individual in this group. The observed hyperlipemia could result, for example, from a defect in lipoprotein lipase activity as reported in idiopathic hyperlipemia, or from alterations in fat metabolism secondary to diabetes.[17] Another possibility may be envisioned in the overproduction of triglyceride from free fatty acid as described in the last portion of the cycle. Finally, it can be stated that the development of atherosclerotic disease may be related directly to an alteration in triglyceride metabolism or related indirectly through elevation of serum cholesterol levels associated with the high serum triglycerides.[18]

The relationship between fasting levels of triglyceride of low-density lipoprotein and the response to the ingestion of fat is important in the interpretation of this study. Elevated fasting levels probably result from the same defect which is expressed by the intolerance to a fat load. The facility with which dietary fat could be handled would depend in part upon the size of the

endogenous pool of lipid prior to the addition of an exogenous source. With high levels of circulating triglyceride the further addition of neutral fat would result in an abnormal response. This situation would be analogous to the use of the glucose-tolerance test in the presence of hyperglycemia. The glucose-tolerance test provides new information only when employed in the presence of minimal or borderline elevation of blood sugar. Previous studies of lipid handling have not been evaluated in relation to the fasting endogenous pool but this deserves consideration in future studies of this type. A decrease in the fasting levels of lipid may be related to the apparent improvement of fat tolerance in individuals who are following a diet restricted in fat. A decrease in the amount of endogenous circulating lipid would decrease the total load on the lipid transport system when an exogenous source of fat is added. This decrease in the total load of fat would facilitate handling of the lipid.

Summary

A fat tolerance test has been used to measure alterations in lipid transport in normal individuals and in patients with ischemic heart disease. Serum lipoproteins and cholesterol were measured after the ingestion of 120 Gm. of butterfat. Greater elevations of the triglyceride containing Sf 20-100 and Sf 100-400 fractions were noted in patients with heart disease and in normal hypercholesterolemic individuals. The implications of these differences are discussed with relation to the presence of a basic metabolic difference in these individuals.

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A technique for the study of cardiac arrhythmias

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A problem encountered in the case of cardiac arrhythmias is that often the disturbance of rhythm has ceased before the patient can report the incident, and thus, an opportunity to make an electrocardiograph recording has been lost. Devices which could be used to record continuously over a period of several hours, or even a day, would be valuable in some instances, in that events in the cardiac cycle of infrequent occurrence could be recorded. With this in mind an arrangement was made to record the electrocardiogram by means of a magnetic tape recorder. One arrangement was to use a continuously recirculating tape whereby the recording could be maintained with little attention but could be stopped after any clinically recognizable event of interest had occurred. The other arrangement was to use a series of tapes with a half hour recording time. Any portions of the tape record which proved to be of interest could be demodulated and played back through a suitable amplifier into a pen recorder and a permanent record obtained.

An additional use which could be made of electrical changes recorded by means of a tape recorder is that these may be translated to a permanent form in a variety of ways, using different degrees of amplification and different rates of movement of the recording paper. Thus, the type of record made from one and the same electrocardiographic complex can be varied to suit the purpose for which the record is required.

Method

The record unit has been kept small and simple to facilitate ward use. The transistor type of electrocardiographic amplifier with a differential input stage and internal dry batteries amplifies the electrocardiogram to about the 1 volt level. An internal calibration system is provided to supply the standardization pulses to the input of the amplifier. The output of the amplifier is taken by a shielded cable to the frequency modulator, which converts the voltage-varying signals to corresponding frequency varying signals.

The modulation unit is built together with power supply, direct coupled (dc) amplifier, and long persistence monitor cathode-ray tube in a single unit. The dc amplifier is used to bring the signal from the electrocardiographic amplifier up to a suitable level to frequency modulate a multivibrator running at a frequency of 2.2 kilocycles (kc.) per second. This frequency modulated (fm) signal is mixed

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with 100 cycles per second (c.p.s.) sine wave obtained from the 50 c.p.s. mains, passed through a filter with a downward sloping response starting at 5 kc. and recorded on a magnetic tape recorder.

With a 2-millivolt signal which is symmetrical around the isoelectric line the frequency deviation is about 1 kc. on either side of the 2.2 kc. center frequency. The presence of a suitable electrocardiographic trace, together with its level of modulation, can be checked on the calibrated monitor cathode-ray tube (Type DP 7/5). To reproduce the recording, the signal from the tape recording is fed into an amplifier with two outputs. One has a filter sharply tuned to 100 c.p.s. to separate the 100 c.p.s. sine wave, which is squared and scaled to produce time pips spaced at 0.08 of a second. The second output is passed through a high-pass filter and then limited. The leading edges of the resulting fm signal are used to trigger a monostable multivibrator. In this manner, each cycle of the fm signal feeds a constant amplitude pulse into a double-diode storage circuit. The recovered electrocardiographic signal is now amplified by a dc amplifier and displayed on a long-persistence cathode-ray tube (DP 13-34). An additional dc channel is used to amplify the time pips. Each of these dc amplifiers is provided with power cathode follower outputs to drive a twin channel pen recorder.

Care must be taken to record an electrocardiogram with as little interference as possible if greater than standard magnification of the reproduced trace is required. It must be remembered that the resolution of the small monitor screen on the modulator unit will not show interference on the isoelectric line that is very much apparent on a reproduced trace at three or four times the standard amplitude.

Results

Similarity of tracings obtained directly and through the intermediation of a magnetic tape recorder. The upper trace of Fig. 1 shows a Lead I record obtained directly from a normal human subject and played directly into a Sanborn (Viso-Cardiette) electrocardiograph; in the lower trace of Fig. 1 a similar record registered on a tape recorder was then played back into the Sanborn electrocardiograph. It will be seen that the two traces are virtually identical.

Advantages of tape recording in the examination of particular complexes. Tape recordings were made during a period of up to an hour or more, and subsequently played back so that the record could be observed visually on an oscillograph screen. A selection was made of any parts of the trace which proved to be of interest, and from these parts the desired number of permanent records were made. Electrocardiographic complexes of especial interest were recorded with various amplification and recording paper speeds in order to bring out particular features. An illustration of the method follows.

We have been interested for some time in the phenomenon of very premature R waves interrupting the T wave of the antecedent complex.[3] In some instances, although one may strongly suspect that a T wave has been interrupted, it is difficult to prove this, or when interruption has evidently occurred it is difficult to identify the exact point on the T wave at which the interruption occurred. It helps if comparison may be made with a complex which is virtually identical with the com-

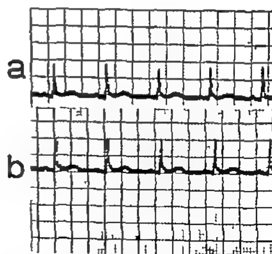


Fig. 1. Electrocardiographic traces (Lead I) from the same individual, *a*, taken in the normal way on a Sanborn Viso-Cardiette electrocardiograph and *b*, first registered on a magnetic tape recorder then played back into the Sanborn electrocardiograph. Time markings in this figure are spaced at 0.04 second.



Fig. 2. In *b* the premature ventricular electrocardiographic complex is interrupted just after the peak of its T wave (*see arrow*) by a second, very premature ventricular systole. In *a* and *c* the premature ventricular systoles are similar to that shown in *b* but they are not interrupted by second premature systoles. The left vertical line passes through the start of the ventricular complexes and the right vertical line passes through the peaks of the T waves. The sharp bend on the descent of the T wave in *b* indicates the point of interruption. Time markings are at 0.08 second.

plex considered to have been interrupted by a premature impulse. Tape recording permits a long record to be made and increases the chance of finding such a complex.

It has been shown [3] that T wave interruption is often observed during the stage of chaotic rhythm which precedes sudden death by ventricular flutter or fibrillation. When a new wave of excitation arises before repolarization is complete in all parts of the heart the new wave is likely to encounter some cardiac muscle which is capable of responding and other muscle which is refractory. The stage is often set for re-entry. Very early interruptions of the T wave are particularly likely to favor such an event. The phenomenon of T wave interruption is best seen when the new wave of excitation takes off in the direction opposite to the descent of the T wave.

A patient who had suffered from congestive heart failure, right bundle branch block and auricular fibrillation had on occasion shown an interruption of the T wave of one complex by a ventricular premature systole. Since this phenomenon is unusual in cases of bundle branch block, we wanted to obtain examples of additional interrupted complexes. Because the phenomenon occurs infrequently it would have been uneconomical to make a continuous long recording on paper. By recording first on tape several examples of the phenomenon were obtained and the interesting parts of the tape were recorded on paper. Fig. 2,*b* shows what appears to be an interrupted T wave. The trace has been reproduced at the standard voltage

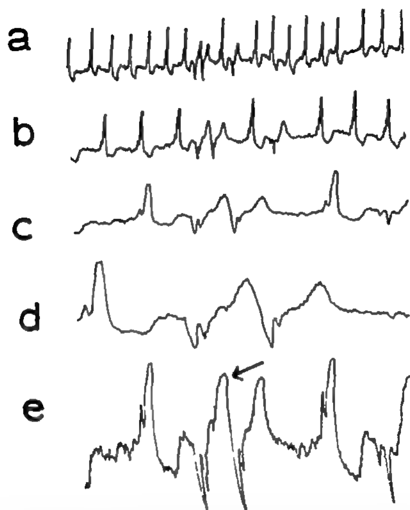


Fig 3 One nd the same pair of ventricular complexes referred to in Fig 2,b ha ing been registered in the first place on the tape recorder may now be converted to permanent records by means of different voltages or paper speeds in order to bring out special features. The three recordings of the pair of complexes are inscribed t varying speeds nd oltage amplifications. It will be noted that the point of interruption (*arrow*) is uncertain in and *b* perceptible in and *d* nd clear in

of 1 cm equals 1 mv and at a rate of 50 mm per second Although t seemed clear that an interruption had taken place just a little after the apex of the T wave, we wanted to compare the interrupted complex with a similar complex which was not interrupted A search was made for similar but uninterrupted complexes, which when found were recorded

In Fig 2,*a* and *c* two uninterrupted complexes have been cut out and pasted one above and one below the interrupted complex making it evident that the point of interruption is likely to be just after the apex. The exact point of interruption however is not so clear as we would like it to be and other recordings were made with different paper speeds and voltage amplifications (Fig 3) One of these traces (Fig 3,*e*) *shows clearly that the point of* interruption is just immediately after the apex of the T wave at the point marked with an arrow For recording the periodicity of phenomena which occur infrequently slow paper speeds can be used as in Fig 3,*a*

The idea of recording biologic phenomena on tape is not new although we have not discovered reports of examples of the

particular use we have made of it. The equipment has been constructed inexpensively in our own laboratory.

Summary

1. A method of recording electrocardiographic phenomena on magnetic tape has been described.

2. The equipment provides a simple and inexpensive way of obtaining a record of cardiological phenomena of infrequent occurrence and is of particular value in the case of certain arrhythmias. Suitable parts of the tape are recorded on paper using a direct writing machine.

3. Records may be obtained which are virtually identical with conventional records; alternatively selected portions of a trace may be made into a permanent record with different characteristics from one and the same set of electrocardiographic complexes.

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The effect of local injection of drugs on the uptake and excretion of intradermally injected dye. Evidence of an extrarenal action of mercurial diuretics

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Observations that an increased flow of fluid from needle tracts of paracenteses and from modified Southey tubes in edematous legs sometimes follows parenteral administration of mercurial diuretics prompted investigation of the local action of these drugs. It has also been observed that a rise in venous pressure occurs within 15 minutes after the parenteral administration of meralluride followed by a fall after diuresis begins. The early increase in venous pressure and changes in hemoconcentration suggest an extrarenal action of the drug since little or no renal effect has occurred by this time. Early investigators[3] considered renal and extrarenal actions of mercurial diuretics, as exemplified specifically by Tezner's observation that saline injected subcutaneously was absorbed more rapidly when a mercurial diuretic had been administered previously. In later reviews on the mechanisms of action and application Ray and Burch[4,5] cited additional support for the possibility that extrarenal effects may influence the diuretic action. Beutner's evidence that mercurial diuretics have local detoxifying action in inhibiting the effects of locally injected convulsants,[6] and the numerous reports of toxic effects of mercurial diuretics on the skin, heart, and other organs also indicate that it is unlikely that even the therapeutic effects of these drugs are limited to one organ, the kidney. In some reports,[7] however, an extrarenal action has been summarily dismissed on the basis of the work of Govaerts[8] and Bartram. Although these investigators established the renal action, they did not exclude extrarenal effects. Other discussions have made little or no reference to the role of extrarenal pharmacologic action of mercurials in the reduction of edema.[1-11] The question of extrarenal effects of mercurial diuretics, therefore, has remained a debatable one.

During visualization of lymphatics for cannulation[12] and studies of rates and patterns of the spread of vital blue dyes in edematous and nonedematous extremities in man,[13] it was observed that the spread of Evans blue (T 1824) avoided the site of a previous needle puncture. In similar studies with patent blue V, Hudack and McMaster[1] had reported decreased

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particular use we have made of it. The equipment has been constructed inexpensively in our own laboratory.

Summary

1. A method of recording electrocardiographic phenomena on magnetic tape has been described.

2. The equipment provides a simple and inexpensive way of obtaining a record of cardiological phenomena of infrequent occurrence and is of particular value in the case of certain arrhythmias. Suitable parts of the tape are recorded on paper using a direct writing machine.

3. Records may be obtained which are virtually identical with conventional records; alternatively selected portions of a trace may be made into a permanent record with different characteristics from one and the same set of electrocardiographic complexes.

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trols for the effects of drugs. Since the influence of changes in the status of edema in an individual on dye excretion was demonstrated in those experiments, data from subjects who were not in a steady state were discarded

Results

A Local clearing of dye Although 3 different dyes were used in this group of experiments, the results were similar in all studies. In some subjects it was not possible to measure an exact area of clearing since the drugs were injected so close to the edge of the dye wheal that only a portion of a cleared circle was enclosed in the dye area In all 8 studies, however the photographic appearances of the discernible portion of each cleared area for each drug or control procedure were similar to those illustrated Since the results were consistently repeatable a number large enough for statistical analysis was not accumulated The best demonstrations were obtained in those in which T 1824 was injected intradermally 24 hours prior to the injection of drugs. Typical examples are presented in Figs. 1 and 2 Examination of the original color transparencies and of black and white reproductions revealed that meralluride was associated with the most complete and permanent clearing of dye from an area. A small vesicle which may be seen on the photographs, appeared after 15 minutes at the site of injection of theophylline ethylenediamine Although on some occasions histamine produced a greater area of clearing some blue dye returned to this area before ultimate fading of the entire blue wheal Progressively less clearing was produced by theophylline ethylenediamine mercaptomerin hyaluronidase epinephrine needle puncture, and saline This relationship is presented graphically in the plots of the calculated clearing factors in Figs. 3 and 4

That the clearing effect of these drugs was not due to chemical bleaching of the dyes was demonstrated by the fact that there was no change in the color of PBV DSB or T 1824 when mixed with each drug and allowed to stand for 3 weeks in vitro

B Urinary excretion of PBV The results of the studies of urinary excretion of patent blue V after intradermal injection of the dye and a drug are summarized in Fig 5 The injection of meralluride intradermally *immediately and into the same site as the* dye was accompanied by an increase in urinary excretion during the first 150 minutes in 3 of 5 nonedematous subjects and in 4 of 5 edematous subjects. The 24-hour recovery of PBV was elevated in all with the exception of one nonedematous subject. Meralluride intravenously in an edematous subject was the only other injection accompanied by a marked increase in urinary excretion of dye An example of various studies in the same subject on different occasions is presented in Fig 6 illustrating the time-course of urinary excretion of PBV for the first 400 minutes after intradermal injection of dye and drug It is assumed that the small quantity of drug (0 05 ml) injected intradermally produced no effect on the kidney and that a local action at the site is responsible for the greater elimination of dye in subjects who received meralluride intradermally

Discussion

These data demonstrate that there is a local extrarenal action by meralluride on the uptake and excretion of vital blue dyes. The evidence for a local action of mercaptomerin is not nearly so conclusive. After initial observations on the clearing of T 1824 from the dye spread area it was considered that the theophylline in meralluride was responsible for the differences in local effects of the two mercurial diuretics. This hypothesis was not confirmed by studies of urinary excretion however for when theophylline ethylenediamine was injected with PBV there was no increase in urinary excretion Thus, these data offer no explanation for the differences. Although DeGraff and Batterman [6] and many years of clinical observations have demonstrated that the addition or combination of theophylline with organic mercurials decreased local toxic actions in our studies theophylline ethylenediamine in concentration and quantity similar to the theophylline in the meralluride administered produced a small vesicle. Lehman reported noticeably less necrosis produced by subcutaneous injection of mercaptomerin in rats than by other organic mercu

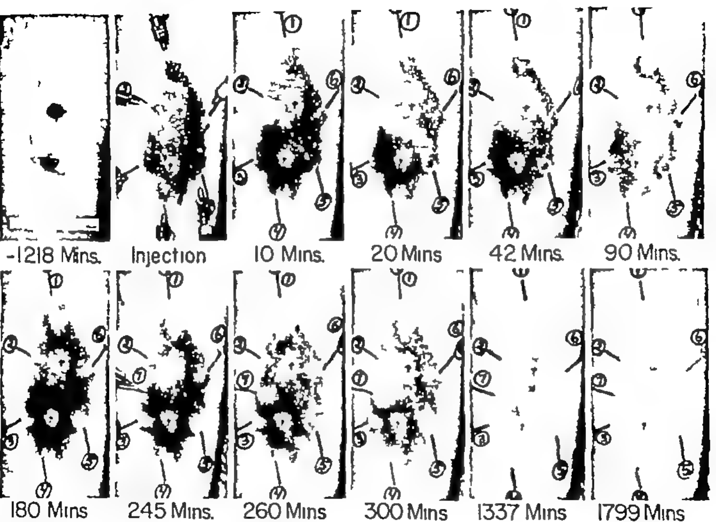


Fig. 1. Clearing of T 1824 from the skin of the forearm of normal male, Subject N 73 after I tradermal I jection of drugs. Minutes indicated below each photograph are relati to time of injection of drugs. N mbered indicators on the rm ignify injection sites (*1*) meralluride, (*2*) dry 30-ga ■ needle (*3*) mercaptomerin, (*4*) saline (*5*) theophylline ethylenediamine, (*6*) hyaluronidase, (*7*) histamine (between *2* nd *3*) I jected 245 minutes after others. Clearing was greatest I the area of injection of meralluride, which cleared the entire upper portion of the dye wheal. Note that blue dye had returned t the area of histamine injection (*7*) by the next day. The tw clear areas within the dy wheal are around the 30-gauge needle punctures made f r i jection of dye 24 hours previously

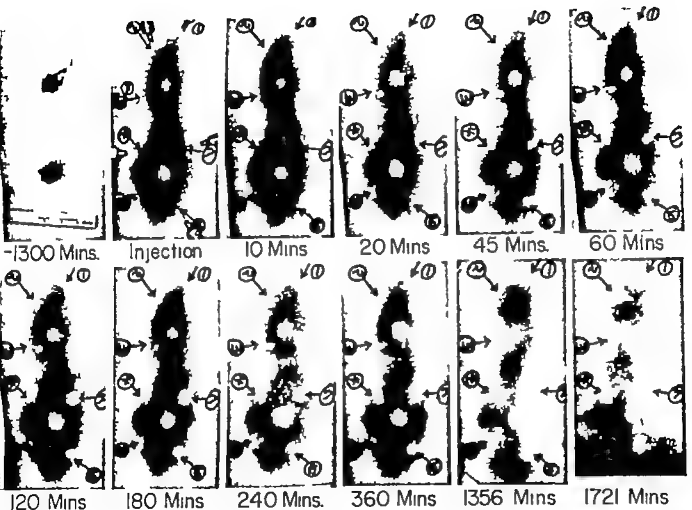


Fig. 2. Clearing of T-1824 from the skin of the forearm of a normal male Subject N. 80. The results and description are similar to those in Fig. 1. The injection sites are numbered (*1*) dry 30-gauge needle (*2*) saline (*3*) epinephrine (*4*) mercupturin (*5*) histamine (*6*) theophylline ethylenediamine (*7*) mersalyl. Visual evaluation of the photographs conforms with the more objective presentation of "clearing factors" in Figs. 3 and 4. Except for an early period during which histamine produced a greater area of clearing to which dye returned, the most distinct and permanent clearing was associated with mersalyl.

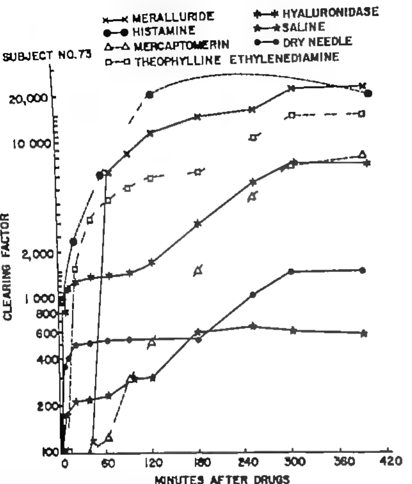


Fig 3 Semilogarithmic plot of the time-course of learing factors for sites of injection of drugs l control Subject No. 73. Clearing factors were calculated by: Area X " learing See text.

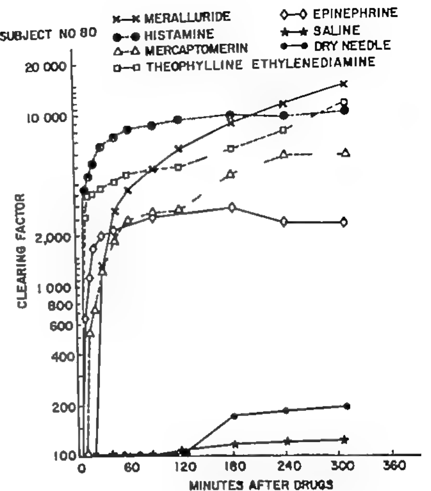


Fig 4 Semilogarithmic plot of the time-course of learing factors l the forearm of c trol Subject N 80 The explanation l the same that for Fig 3

nal diuretics including meralluride. The effects shown in his photographs have not been observed in our clinical or experimental experience. Our results do agree however that there is a difference in local effects of mercaptomerin and meralluride.

Partial explanation for the mechanisms of clearing of dye areas by the drugs and for increased urinary excretion of PBV associated with locally injected meralluride may be found in the experiments of Cocchiara who placed dyes and drugs in the vicinity of vessels on the inner surface of abdominal skin flaps in rats and observed uptake by vessels microscopically. Meralluride caused an increased uptake of PBV, DSB and T 1824 primarily by capillaries and venules, and occasionally by lymphatics in 33 of 37 observations. Mercaptomerin produced a slight increase in uptake in only 5 of 39 observations. Mercuric chloride 39 mg per milliliter prevented uptake. Histamine was accompanied by a decreased uptake in 37 of 39 observations and produced a diffusion of fluid from the vessels, diluting the dye in the area. The dilution and the increase in local pressure which force movement of stained interstitial fluid are assumed to be partially responsible for the appearance of clearing in the skin of man. Theophylline ethylenediamine caused a slight increase in uptake in but 4 of 27 observations in rats and produced diffusion of fluid from vessels and dilution of dye in the area, similar to the effects of histamine. In human subjects the increased tissue pressure persisted for a longer time in the vicinity of the vesicle produced; therefore, blue fluid did not return to the site so readily as in the area of histamine injection. Hyaluronidase was accompanied

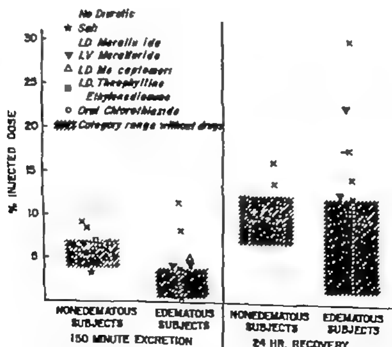


Fig. 5. Urinary excretion of PBV after test substance. *I.D.*, Intradermal injection of 0.03 ml. of test substance. *I.V.*, Intravenous injection of 2 ml. The shaded blocks cover the range of values obtained from numerous subjects who received no drugs in a previously reported series, and who were used as controls for this study. In the edematous group, the subject who received mercaptomerin demonstrated a slight increase in 150 minutes of cumulative excretion but fell within the control range for 24-hour recovery. The subject labeled — X excreted little in the first 2½ hours but exceeded the control rate for edematous subjects after that time. Intravenous meralluride increased excretion in the edematous group but not in the nonedematous subject studied in this manner.

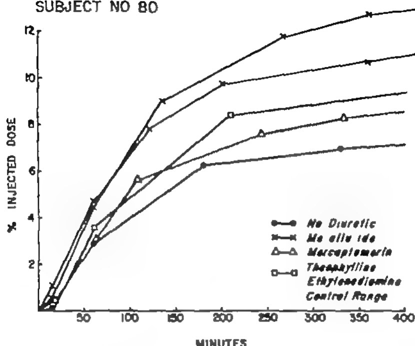


Fig 6 An example of results in Subject No. 80 in whom excretion of PBV was studied on several occasions after intradermal administration with various drugs The shaded area covers the range of time-courses of excretion for the control group. Increased excretion associated with meralluride is apparent

by a slight increase in uptake in 10 of 42 observations, apparently because of spreading and exposure of dye to more vessels. In skin flap preparations in which vessels were observed after systemic administrations of drugs intramuscular mercaptomerin showed no influence on the uptake of dye by capillaries Intravenous theophylline ethylenediamine did not increase uptake and was associated with diffusion from vessels. As with the local application meralluride intravenously was accompanied by an increased uptake of dye by capillaries, indicating that sufficient quantities reached the tissues to produce the local effects. Distribution of from 20 to 50 per cent of labeled meralluride into extrarenal tissues between 5 and 60 minutes after intravenous administration supports this concept for man

It is apparent that there are two factors responsible for the appearance of clearing of dye from a local area (1) increased diffusion of fluid from capillaries accompanied by increased local tissue pressure and by dilution of dye, and (2) increased uptake by local vessels. The dilution of dye by diffusion of fluid from vessels is associated with exposure to theophylline ethylenediamine histamine and light local trauma, interpreted as a histamine effect. This mechanism of clearing is not presumed to be effective in increasing urinary excretion of dye or other tissue substances The increased local uptake associated with exposure to meralluride may be of significance in the explanation of the observed increased urinary excretion of dye.

Summary

Clearing of vital blue dyes from the site of intradermally injected drugs, and increased urinary excretion of intradermally injected patent blue V with drugs have demonstrated that meralluride exerts a local extrarenal action at the tissue level apparently by increasing the uptake of dye by capillaries, small veins, and lymphatics. Other cardiovascular drugs studied did not exhibit all of the same effects but did manifest evidence of local actions of different nature, for example, increased diffusion of fluid from capillaries. These findings contribute to a better understand

ing of the actions of mercurial diuretics and confirm the existence of an extrarenal action of meralluride which may be of significance in the treatment of edema.

Although more detailed basic techniques are necessary to determine the precise mechanism of action at cellular levels the techniques presented in these studies can serve as methods for establishing the existence of local effects of other pharmacologic, chemical or physical agents.

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The effect of Na_4EDTA induced hypocalcemia upon the general and coronary hemodynamics of the intact animal

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The importance of calcium in cardiac contraction has been appreciated for many years[1] and some work has been reported concerning the effect of this ion upon coronary flow.[2,3] The studies quoted, carried out in isolated hearts, claimed to demonstrate coronary vasodilation both for hypocalcemia and added calcium. With this knowledge, and having regard to the clinical use of chelation-induced hypocalcemia in cardiac arrhythmias, we decided to investigate the general and cardiac effects of Na EDTA induced hypocalcemia in the intact anesthetized dog.

Material and methods

Ten dogs, unselected by age, breed, or sex, were used. They weighed between 10 and 24 kilograms and seemed to be healthy at the time of study.

The animals were premedicated with morphine sulfate, 3 mg. per kilogram, given subcutaneously. This was followed in 1 hour by the intravenous injection of Dial-urethane-Nembutal,* in a dose of 0.25 ml. per kilogram of body weight. A cuffed endotracheal tube was introduced and the animal connected to a Tissot spirometer for collection of expired air. A system of valves allowed a rapid change from room air to a mixture of nitrous oxide (15 per cent), nitrogen (64 per cent), and oxygen (20 per cent).

By way of the neck veins and under fluoroscopic control, standard cardiac catheters were placed in a main branch of the pulmonary artery, and in the coronary sinus. The position of the latter was confirmed by its characteristic x-ray silhouette and by the aspiration of blood which had a much lower oxygen content than that of the pulmonary artery. A Cournand needle was placed in a femoral artery. Pressures were measured by strain gauge, electrically integrated for mean values, and recorded on a direct writing machine.

Cardiac output was measured by the Fick principle; expired air analysis was done in the Scholander apparatus. Samples of blood were analyzed for oxygen and carbon dioxide in the Van Slyke machine. Coronary blood flow was measured by the

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*Courtesy CIBA, Australia. It contains Dial, 100 mg./ml.; monoethylurea and urethane, each 400 mg./ml. Nembutal, 60 mg./ml. was used as 1:1 diluent.

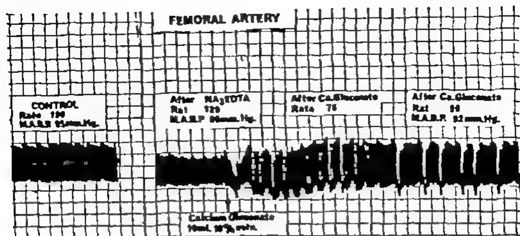


Fig. 1. The effect of calcium gluconate upon Na_2EDTA-induced hypotension and tachycardia.

Fick principle using the nitrous-oxide saturation method. Works and resistances were derived by accepted methods.

Control values for cardiac output and coronary blood flow were obtained 1 hour after the intravenous anesthetic. These values compared well with the figures previously reported from this laboratory. Thirty minutes after the control measurements hypocalcemia was induced by the intravenous injection of trisodium EDTA; the total dose given was 62.5 mg. per kilogram. This was dissolved in 20 ml. of saline; of this 5 ml. was given in 2 minutes, and the remainder at the rate of 1 ml. per minute.

Calcium was estimated by a modification of the method of Clark and Collip;[4] the test solutions were read on a flame photometer and also by spectrophotometry. Comparison of the methods showed no significant difference. Sodium and potassium were measured by flame photometry. A Cambridge instrument was used to measure pH.

Results

All figures given are group means with standard deviation; statistical examination of the differences of the means was made by Student's *t* test, significance (statistical, if not physiological) being accepted at the 5 per cent level.

Values for serum ions. The values for serum ions are shown in Table I. The animals showed a significant reduction in total calcium. The increase in serum sodium is presumably due to the use of a sodium salt of EDTA. There is a reduction in the ratio Ca/Na + K.

General metabolism. Table II shows that significant changes occurred in the minute volume of respiration and in tidal volume. The production of carbon dioxide increased more than did the consumption of oxygen so that the exchange ratio (R.Q.) was augmented. The only significant changes in blood gas content relate to reductions in carbon dioxide. The values for pH and hemoglobin were unchanged. The maintenance of hematocrit at control values does not suggest any evidence of hemodilution.

Pressure work responses. Table III shows that cardiac output was maintained but that a significant increase in heart rate reduced stroke volume. Pressures decreased in the pulmonary and systemic circuits, but no statistically significant changes were observed in the associated ventricular works or vascular resistances.

Table I. Serum ions (milliequivalents per liter)

Factor	Control	Experimental
Sodium	139.2 ± 4.4	146.0 + 8.5
Potassium	4.3 ± 0.9	4.1 ± 1.0
Calcium	5.0 ± 0.7	3.7 ± 0.7
Ratio Ca/Na + K	0.0358 ± 0.0028	0.0261 + 0.002

*p value of change 0.05 or less. Figures are means with S.D.

Table II General metabolism

Factor	*Control*	*Experimental*
Respiratory olume (L. min)	3 4 ± 0 9	5 0 ± 2 4
Respiratory t min	21 ± 8	25 ± 10
Tidal volume (ml)	171 ± 86	232 ± 126
Oxygen consumption (ml min)	109 ± 31	125 ± 64
Carbon-dioxide production (ml min)	81 ± 21	103 ± 46
Respiratory quotient	0 74 ± 0 09	0 82 ± 0 08
Arterial O_2 content (ols %	16 4 ± 2 3	16 1 ± 1 8
Mixed enous O_2 content (ols.)	11 5 ± 2 7	10 9 ± 2 3
Δ Arterial-mixed enous O content (ol)	4 9 ± 1 6	5 1 ± 0 9
Mixed enous CO_2 (ols)	51 6 ± 5 5	48 7 ± 6 8
Arterial CO content (ols)	48 1 ± 7 2	45 0 ± 7 7
Δ Mixed enous-arterial CO content (ols)	3 5 ± 1 8	3 7 ± 1 5
Hemoglobin (Gm.)	14 6 ± 1 5	14 6 ± 1 2
Hematocrit	44 ± 4	44 ± 5

*p alue of change 0 05 or less.
Figures are means with S D

Table III P essure work responses

Factor	*Control*	*Experimental*
Cardia output (L min.)	2 3 ± 0 5	2 5 ± 1 1
Heart rate min	93 ± 29	136 ± 23
Stroke olume (ml.)	26 ± 9	11 ± 8*
Femoral pre ure (Mean, mm Hg)	179 ± 15	116 ± 15
Pulmonary arterial pressure (Mean, mm. Hg)	13 ± 4	11 ± 4
Lef entricular work (kg M /min.)	4 0 ± 1 0	3 9 ± 1 8
Right entricular work (kg M./min.)	0 33 ± 0 14	0 37 ± 0 24
Total peripheral resistance (Calculated d nes/sec /cm.$^{-5}$)	4 794 ± 1 363	3 972 ± 1 682
Total pulmonary resistance (Calculated dynes/sec./cm.$^{-5}$)	441 ± 191	387 ± 205

*p value of change 0 05 or less.
Figures are means with S D

Table IV Coronary hemodynamics myocardial O and CO metabolism and cardiac efficiency

Factor	*Control*	*Experimental*
Coronary blood flow (ml. 100 Gm. heart/min.)	91 ± 21	112 ± 31
Coronary flow per beat (ml)	1 02 ± 0 26	0 86 ± 0 21
Coronary ascular resistance (units)	1 4 ± 0 2	1 0 ± 0 3
Ratio — Coronary flow/left entricular work	24 ± 8	33 ± 15
Coronary sinus O_2 content (vols %)	5 0 ± 2 7	3 9 ± 2 0*
Δ Arterial-coronary sinus O_2 (vols.)	10 9 ± 1 2	12 1 ± 1
Coronary sinus CO content (vols.)	57 0 ± 7 0	54 0 ± 7 1
Arterial CO_2 content (flow) (vols. %)	48 9 ± 6 5	44 0 ± 7 0*
Δ Coronary sinus-arterial CO_2 (ols. %)	8 2 ± 1 8	10 0 ± 2 5
Cardiac respiratory quotient	0 75 ± 0 09	0 84 ± 0 19
Cardiac metabolic rate—O (ml./100 Gm. heart/min.)	9 9 ± 2 7	13 5 ± 3 7
Cardiac metabolic rate—CO_2 (ml./100 Gm. heart/min.)	7 4 ± 2 2	11 6 ± 4 3
Index of efficiency (left ventricular work/C.M R. O_2)	0 42 ± 0 14	0 33 ± 0 25

*p value of change 0 05 or less.
Figures are means with S.D.

Coronary hemodynamics myocardial O and CO metabolism and cardiac efficiency (*Table IV*) Coronary blood flow showed a moderate but statistically significant increase However the effect of the tachycardia was to decrease stroke coronary flow Cardiac extraction of oxygen increased as did cardiac usage of oxygen Similar trends were seen for cardiac carbon-dioxide metabolism Apparent cardiac efficiency (index of efficiency") declined

Comment

The animals showed a reduction in total calcium (Table I) Additional experiments had shown that serum ultrafiltrate was reduced in calcium content beyond that amount due to the completed (not protein bound) moiety This reduction is presumably due to a decrease in ionized calcium The contemporaneous decrease in serum calcium indicates that protein-bound calcium is also reduced. In other words Na$_2$ EDTA induces a new equilibrium in which both ionized and protein bound calcium are reduced Since there is no evidence that protein bound calcium has hemodynamic effects, it is presumed that the hemodynamic changes now reported are due to a decrease in ionized calcium. This latter is reflected in the levels of total calcium shown in Table I

The role of magnesium in hemodynamics is not quite clear In order to exclude changes in magnesium as a factor in the hemodynamic situation here reported we rendered dogs hypocalcemic and hypotensive with Na EDTA. No changes in serum magnesium (measured by flame spectrophotometry) were evident In addition the hypotension and tachycardia could not be reversed by the injection of 10 per cent Mg SO_4 but they did revert toward normal when calcium gluconate was administered.

However another fundamental question is whether the results described here are due to a reduction in calcium or to the injected EDTA thus, the results quoted by Leitch and Haley[8] seemed to suggest that any EDTA derivative would cause coronary vasodilatation—at least in the isolated heart Therefore two further experiments were made First dogs prepared as already described were made hypocalcemic with trisodium EDTA tachycardia and hypotension resulted (cf Table III) Thereupon an amount of calcium calculated to correct the deficit was given A typical result is shown in Fig 1 this would appear to suggest that the changes in pressure and rate are reversible by calcium this implies that these changes in the primary experiment were due to hypocalcemia

Table V Effect of calcium versenate (65 mg /Kg) upon eight dogs

Factor	*Control*	*Experimental*
Heart rate	95 ± 10	102 ± 15
Systemic pressure (Mean mm. Hg)	135 ± 13	137 ± 19
Pulmonary arterial pressure (Mean, mm. Hg)	14 0 ± 2 4	12 6 ± 1 6
Δ Arterial-mixed venous O_2 (vols. %)	3 5 ± 0 9	3 6 ± 1 0
Δ Mixed venous-arterial CO (ols. %)	2 5 ± 1 0	3 2 ± 1 7
Cardiac output (L./min.)	3 4 ± 1 3	3 3 ± 1 4
Coronary blood flow (ml /100 Gm. heart/min.)	87 ± 15	90 ± 18
Δ Arterial-coronary sinus O_2 (ols. %)	10 0 ± 1 1	10 8 ± 1 4
Δ Coronary sinus-arterial CO_2 (vols. %)	7 6 ± 1 8	8 4 ± 1 8
Cardiac metabolic rate—O_2 (ml /100 Gm. heart/min.)	8 7 ± 0 6	9 7 ± 0 5
Cardiac metabolic rate—CO_2 (ml./100 Gm heart/min.)	6 6 ± 1 8	7 6 ± 2 4
Hemoglobin (Gm. %)	13 4 ± 0 9	13 0 ± 0 8
pH (Arterial)	7 34 ± 0 05	7 36 ± 0 05
Sodium (mEq /L.)	143 ± 5	145 ± 6
Potassium (mEq./L.)	4 32 ± 0 28	4 30 ± 0 26
Calcium (mEq /L.)	4 74 ± 0 44	4 96 ± 0 32

*p value of change 05 or less.
Figures are means with S.D

Another experiment was carried out exactly as described in the foregoing section on methods with the exception that calcium versenate (Na Ca EDTA) was substituted for trisodium EDTA Suffice it to say that no significant changes were found except for a minor although statistically significant fall in mean pulmonary arterial pressure Calcium versenate maintained serum calcium at control value The complete results are given in Table V

It is difficult therefore to avoid the conclusion that the results described for trisodium EDTA are due to anything other than the induced hypocalcemia Weight is added to this conclusion by the findings of Surawicz and associates[9] who described a depression of systemic blood pressure in human subjects given disodium EDTA in a sufficient quantity regularly to depress the serum calcium no such response was seen by them when patients were given calcium versenate

Discussion

The increase in respiratory exchange with hypocalcemia appears not to have been described previously This would tend to explain the increase in the production of carbon dioxide which in turn is the prime determinant of the increase in the respiratory quotient These are changes which do not occur spontaneously in this preparation The more striking changes are in the heart rate and systemic pressure the reduction in the mean (and systolic) pressures may be equated perhaps, with a decrease in contractility[4] the work of each ventricle was maintained Hypocalcemia cannot be said to act as a systemic or pulmonary vasodilator

The increase in coronary blood flow is a modest but consistent one and when compounded with the decrease in perfusion pressure it leads to a significant decrease in coronary vascular resistance The increase in the rate of cardiac extraction of oxygen is perhaps the major factor in the increase in the cardiac metabolic rate for oxygen which outstrips the left ventricular work, so that cardiac efficiency declines.

It has been suggested that the coronary flow is related to the heart rate[11] in this study the correlation between these two factors was positively made ($r = 0.5634$ $p = 0.01$) Again the relationship of the product (rate × mean arterial pressure) could be positively correlated ($r = 0.553$ $p = .01$) with the increase in the cardiac oxygen consumption[12] An inverse correlation was found to exist between the levels of calcium and the cardiac usage of oxygen. Of course these correlations are associative and not necessarily causal

It has been said that the contractility of the heart varies with the ratio $C_{Ca}/C_{Na} + C_K$[18] in the present study this ratio decreased significantly (Table I) this was partly because of a decrease in the content of calcium and partly because of an increase in the sodium The relative importance of these ions in the ratio thus calculated from figures derived from the intact animal is unknown although Surawicz, using Na_2EDTA was able to reduce the level of calcium and the blood pressure without showing any change in the level of potassium or sodium It is tempting to conclude therefore that the present diminution in the blood pressure is due principally to a change in calcium and not to other factors such as sodium for example.

The coronary vasodilator activity of hypocalcemia here reported is similar to that reported for the isolated heart but undue comparison would be unwise

Summary

The action of Na_2EDTA-induced hypocalcemia upon the intact animal is reported Respiratory exchange is stimulated cardiac output is maintained but there is a decrease in the pressures in the greater and lesser circuits. Coronary blood flow increases modestly although coronary vascular resistance decreases. There is an increase in the cardiac usage of oxygen and carbon dioxide

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The effect of lanatoside C on coronary vascular resistance

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The results of investigations of the effect of digitalis on the coronary vascular bed are contradictory. Bodo[1] concluded that digitalis and strophanthin produced a moderate increase in coronary flow in the dog heart-lung preparation. Gilbert and Fenn[2] observed a decrease in coronary sinus outflow after the administration of whole-leaf digitalis, digitoxin, and ouabain. When less than 20 per cent of the lethal dose of digilanid A, B, or C was used, Essex and associates[3] found no effect on the coronary artery blood flow measured with a thermostromuhr. Larger doses produced toxicity.

In intact dogs, Ginsberg and associates found that strophanthin, scillaren, digitalis tincture, Digiglusin, and Digifolin reduced coronary sinus outflow. Lindner and Katz[4] concluded that K-strophanthin, ouabain, and Digifolin, in therapeutic doses, have a direct coronary artery constrictor effect in a modified Langendorff preparation. There was no effect on left circumflex coronary artery blood flow when therapeutic doses of Digifolin, Digalen, digitoxin, and lanatoside A were given in the studies of Dearing and associates; however, toxic doses decreased blood flow. Ouabain produced an increase in coronary vascular resistance in both small and large doses in a coronary sinus outflow preparation studied by Page and associates. Sherrod[8] found that intravenous strophanthin G decreased coronary sinus outflow and that this decrease was followed by a marked and sustained increase. Toxic doses of strophanthin increased coronary sinus flow in the studies of Dorner. Frank and associates reported that therapeutic doses of strophanthin, acetyldigitoxin, and digitoxin had no effect on coronary sinus outflow in intact dogs. Strophanthin K was without effect on coronary artery blood flow measured with a rotameter after coronary artery occlusion in the experiments of Szabo.[11] Recently, Lauener and Wander[12] showed that K-strophanthin and digitoxigenin decreased coronary sinus outflow in the cat heart-lung preparation.

In human beings, Fenn and Gilbert[13] observed an increase in angina pectoris with therapeutic doses of digitalis. In a study with control observations, however, this was not confirmed by Gold and associates.[14] In normal and failing human hearts strophanthus did not affect the coronary resistance according to Bing

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and associates.[14] There is no agreement therefore concerning the effect of digitalis on the coronary blood flow and resistance.

This study has three objectives (1) to study the effect of desacetyl lanatoside C hereafter referred to as lanatoside C (Cedilanid)* on the coronary vascular resistance at many rates of blood flow in the physiologic range (2) to differentiate between the effect of the diluent without lanatoside C and the active preparation and (3) to study the normal coronary artery pressure–blood flow relations in the intact animal.

Methods

Seventeen dogs which weighed between 12 and 18 kilograms were anesthetized with 25 mg per kilogram of pentobarbital sodium. A tracheal cannula was inserted and the chest was opened in the fourth left intercostal space. Respiration was maintained using a positive pressure respirator with 100 per cent oxygen. The pericardium was opened and a ligature was passed around the left main coronary artery as it emerged from the aorta. Heparin sodium 200 mg was given intravenously. The aortic pressure was recorded through a cannula inserted into the femoral artery with a Statham 23 Db manometer and a Sanborn Model 150 recorder. A polyethylene cannula attached to a length of Tygon and rubber tubing was inserted into the opposite femoral artery. This tubing was slowly filled with blood from the aorta. A stainless steel coronary artery cannula, at the end of the tubing was inserted into the aorta via a previously isolated left subclavian artery. The tubing was placed in a pump† whose output was calibrated and was independent of pressure in the inflow and outflow tubing over the pressure range studied. The pump was calibrated in duplicate after each experiment. The coronary artery cannula was then guided to the ostium of the left main coronary artery inserted, and tied into place. The blood pressure in the coronary perfusion tubing at the junction with the coronary cannula, was measured with a 20-gauge needle attached to PE 90 polyethylene tubing and a Statham P 23 Db manometer. This pressure was recorded as an electronically integrated mean. The flow of blood through the coronary cannula could be varied by changing the speed of the pump and was adjusted so that the mean coronary artery pressure was equal to the mean aortic pressure. The left intraventricular pressure and ventricular rate were recorded continuously with a P 23 Db Statham manometer via direct needle puncture of the left ventricular wall. A period of 20 minutes was allowed for stabilization of the preparation.

Effect of lanatoside C at different regions of the pressure flow curve. In 10 dogs the effect of lanatoside C on coronary pressure–blood flow relations was studied over a wide range of rates of blood flow in periods 4 through 6. In 6 of these dogs periods 1 through 3 were also studied. The various periods were studied in the sequence described below.

PERIOD 1. A 5 per cent solution of dextrose in water was infused* into the tubing of the coronary perfusion circuit at a constant rate ranging from 0.16 to 0.4 c.c. per minute. The coronary artery pressure was recorded at a blood flow rate at which the mean coronary and mean aortic pressures were identical. This will be referred to as the control flow rate. The coronary blood flow was then increased to two or three higher rates by adjusting the calibrated pump. The flow rate could be reproduced within ±2 c.c. per minute. The flow was then returned to the control rate and was subsequently decreased to two blood flow rates below the control. The flow was finally increased to the control blood flow rate. At each of these blood flow rates the mean coronary artery pressure was recorded after it had stabilized a period of approximately 30 seconds. The intraventricular pressure was recorded continuously. In each experiment five or six flow rates were studied.

PERIOD 2. The identical procedure was repeated using the same flow rates as for period 1. This second control period was used in the analysis of the reproducibility of the pressure flow curves.

*Sandoz Pharmaceuticals, Hanover, N. J., kindly supplied the drug and the diluent.

†Sigmamotor Pump Model T6SH, Middleport, N. Y.

*Constant Infusion Pump, Metro Industries, Long Island City, N. Y.

PERIOD 3. The pressure-flow relations were studied over the entire flow range as described in periods 1 and 2. However, the diluent of the lanatoside C preparation without the active drug was infused into the coronary perfusion tubing. Two cubic centimeters of this diluent added to 8 c.c. of 5 per cent dextrose in water was infused at the same rate as was the 5 per cent dextrose in water in periods 1 and 2.

PERIOD 4. This was another control period identical to periods 1 and 2.

PERIOD 5. Lanatoside C, 0.4 mg. in 2 c.c. added to 8 c.c. of 5 per cent dextrose in water was infused into the coronary perfusion circuit at rates that varied from 0.0064 to 0.016 mg. per minute. The coronary pressure–blood flow relations were studied again as described in the previous periods. The calculated concentration of lanatoside C in the blood perfusing the left coronary artery ranged from 0.0005 to 0.00009 mg. per cubic centimeter. In each experiment the concentration of the drug in the blood perfusing the coronary artery varied inversely with the rate of blood flow, since the dose infused at a constant rate was diluted by the higher blood flow. The lanatoside C was never infused for a period longer than 6 minutes. The dose administered was determined by estimating the blood concentration which would exist in man after the administration of 0.8 mg. of lanatoside C intravenously. The concentration produced by the infusion varied from one half to three times this value.

PERIOD 6. This was a control period identical to periods 1, 2, and 4.

Three flow rates were chosen for analysis from each period, representing different regions of the pressure-flow curve. The mean coronary pressures and the calculated left main coronary vascular resistances expressed as peripheral resistance units (PRU) were compared. The differences in coronary pressure and PRU values were compared at identical rates of blood flow in any one experiment. The coronary pressure and PRU value differences between periods 1 and 2 represent the reproducibility of the pressure–blood flow relations. The differences between periods 2 and 3 show the effect of the diluent compared to a control period. The differences between periods 4 and 5 demonstrate the effect of lanatoside C. The differences between periods 5 and 6 reveal the persistence of the effect of lanatoside C during the last control period.

Data which compare the coronary artery pressures and PRU values in periods 4, 5, and 6 are tabulated in four groups according to flow rate (low, 44 to 85 c.c./min.; medium, 86 to 119 c.c./min.; high, 120 to 144 c.c./min.; and very high, over 184 c.c./min.). The data which compare periods 1, 2, and 3 are arranged in three groups. The low and medium flow rate groups, as described above, are combined. The statistical significance of the data was tested with the *t* test.[17]

Effect of lanatoside C at a single rate of blood flow. The remaining 7 dogs were studied at a single coronary blood flow rate. Of these, 2 were given lanatoside C intravenously in a single dose; in 1 the lanatoside C was given as a single dose directly into the coronary artery perfusion tubing; and in the other 4 dogs, lanatoside C was infused into the coronary artery at a constant rate.

Results

Effect of lanatoside C at different regions of the pressure-flow curve. In all 10 dogs lanatoside C produced an increase in coronary artery pressure at the control rate of blood flow. This occurred within 2 minutes of starting the infusion. The increases in coronary artery pressure and PRU values were statistically significant at all coronary blood flow rates. The effect of lanatoside C is shown in Table I as the difference between period 4 and period 5. During the infusion of the drug the average increase in coronary pressure was 20.7 and 22.5 mm. Hg, respectively, at the low and medium rates of blood flow, and 17.7 and 16.3 mm. Hg, respectively, at the high and very high rates of blood flow. The individual coronary pressure values at the same rate of blood flow before and during infusion of lanatoside C are shown in Fig. 1. The pressure rose in all but three instances. Fig. 2 shows the average pressure-flow curves before and during the infusion of the drug. Lanatoside C displaced the curve toward the pressure axis, indicating an increase in coronary

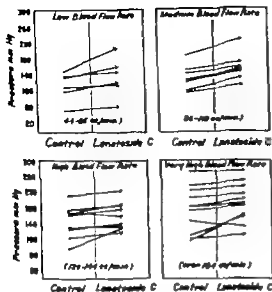


Fig. 1. Shown is the effect of lanatoside C on left main coronary pressure at identical rates of blood flow compared to control observations. Each rectangle represents a different range of blood flow.

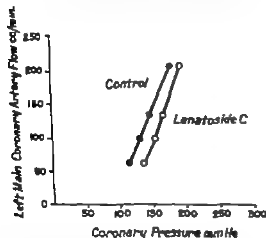


Fig. 2. The average coronary artery pressure–blood flow relations before and during infusion of lanatoside C.

vascular resistance at all regions of the pressure-flow curve. The average pressure-flow curve was relatively straight, in the range studied, and the shape was not significantly affected by lanatoside C. In both the control and lanatoside C periods, the resistance decreased with increasing coronary blood flow. During infusion of lanatoside C the average PRU value in the low medium blood flow range was 1.79, in the high flow range it was 1.23, and in the very high flow range it was 1.00. The differences between the low medium and high and between the high and very high PRU values are significant (.05 > p > .02). During the control period the PRU value in the low-medium flow range was 1.50, in the high flow range it was 1.09, and in the very high flow range it was .91. The differences between these values are less significant (0.1 > p > .05).

Infusion of the diluent had no statistically significant effect on the coronary artery pressure or PRU values, as shown in Table I as the difference between periods 2 and 3. Comparison of periods 1 and 2, both of which were control periods, reveals no statistically significant difference at the high and very high flow rates, but the coronary pressure was 14.4 mm. Hg lower in the second control period at the low-medium flow rate. The differences between periods 5 and 6 seen in Table I also are not statistically significant. This indicates that the effect of lanatoside C persisted during the final control period. The increase in pressure persisted from 20 to 45 minutes after period 6.

In these experiments there were no statistically significant changes in aortic pressure, left ventricular systolic or end diastolic pressure, or ventricular rate. There were no cardiac arrhythmias.

Effect of lanatoside C at a single rate of blood flow. In one experiment intracoronary infusion of lanatoside C raised the coronary artery pressure at a constant flow in proportion to the rate of infusion of the drug. The rate of infusion varied from one half to twice that used in the previously described experiments. Lanatoside C intravenously raised the coronary pressure from 151 to 164 mm. Hg when 0.4 mg. was given to one dog and from 160 to 185 mm. Hg when 0.8 mg. was given to another. This change in pressure occurred within 1 minute of injection.

Lanatoside C diluted in 5 per cent dextrose in water was infused into the coronary perfusion tubing of the 4 remaining dogs at a constant rate of 0.008 mg. per minute. This rate of infusion resulted in an increase in the average coronary pressure of 13 mm. Hg (range 10 to 15 mm. Hg) at a constant rate of blood flow. One cubic centimeter of undiluted lanato-

Table I Summary of flow data

		Flow		Average pressure (mm Hg)	Average pressure (mm Hg)	Average ΔP (mm Hg)	Average ΔPRU	p value Δ pressure
				Period 1	Period 2			
Period 1	period 2	Low and medium	5	125	111	↓ 14	↓ 0.20	.02–.05
Control 1	control 2	High	4	165	165	0	0.00	.9
		Very high	6	195	199	↑ 4	↑ 0.02	.2–.3
				Period 2	Period 3			
Period 2	period 3	Low and medium	5	125	126	↑ 1	↑ 0.01	.8–.9
Control 2	diluent	High	5	170	162	↓ 8	↓ 0.06	.4–.5
		Very high	5	202	196	↓ 6	↓ 0.03	.7–.8
				Period 4	Period 5			
Period 4	period 5	Low	6	116	137	↑ 21	↑ 0.30	.02–.05
		Medium	8	132	155	↑ 23	↑ 0.20	.01
Control	lanatoside C	High	9	147	165	↑ 18	↑ 0.14	.01
		Very high	11	177	194	↑ 17	↑ 0.07	.02–.05
				Period 5	Period 6			
Period 5	period 6	Low	[illegible]	136	136	0	↓ 0.02	.9
		Medium	6	162	154	↓ [illegible]	↓ 0.02	.9
Lanatoside C	control	High	8	169	168	↓ 1	↓ 0.01	.8–.9
		Very high	10	202	177	↓ 25	↓ 0.13	.1–.2

*Number of paired observations.
ΔP Change in coronary artery pressure.
ΔPR Change in PRU value.

side C (0.2 mg.) injected directly into the coronary perfusion tubing increased the coronary artery pressure 55 mm. Hg (from 120 to 175 mm. Hg). This dose was undoubtedly in toxic range. With the exception of the animal in which a toxic dose was used, the aortic pressure, left ventricular systolic and end-diastolic pressures, and ventricular rate did not change significantly during an observation period which lasted 15 minutes. During this period there was no evidence of digitalis toxicity as evidenced by arrhythmias.

Discussion

Lanatoside C has a marked coronary constrictor effect in this preparation. This occurs within 2 minutes after the start of infusion of the drug. This does not occur during infusion of the diluent without the drug. The increase in vascular resistance is not due to a changing state of the preparation, since repeated performance of the pressure-flow curves without the drug produces no increase in resistance. In fact, there is dilatation at low rates of blood flow in some animals when the control periods are repeated. The constrictor effect of the drug persists during the postinfusion period until the experiment is discontinued, a time period between 20 and 45 minutes.

There are many possible explanations for the increase in vascular resistance. One is that lanatoside C has a direct effect on the blood vessels. Its constrictor effect on veins is well known.[18-20] It is quite unlikely that venoconstriction alone could explain an increase in resistance of this magnitude. A constrictor effect on arterioles previously demonstrated on other vascular beds remains a distinct possibility.[21] It is also possible that lanatoside C exerts its effect on the coronary vascular

resistance by increasing the intramyocardial tension. This might be related to its positive inotropic effect. However, the increase in vascular resistance occurs within 2 minutes, a time interval which is shorter than that usually associated with the onset of the positive inotropic action of lanatoside C. The intramyocardial tension was not measured; however, the left ventricular end-diastolic pressure, aortic pressure, and heart rate were unaffected by infusion of lanatoside C. There is no direct evidence concerning the role of this factor in producing the increase in coronary resistance.

Another possible explanation of the increase in resistance is that collateral blood flow might influence coronary vascular resistance in this preparation. When the left main coronary artery is perfused at a low rate of blood flow, blood from the right coronary artery, which is perfused at the aortic blood pressure, might flow through collaterals into the left coronary system, elevating the pressure. However, the increase in vascular resistance was noted in all rates of blood flow. At the high rates of blood flow, collateral flow, if it is at all important, would be from the left to the right coronary vascular bed. Thus, this cannot be a significant factor in producing apparent coronary constriction at the higher rates of coronary blood flow.

At low rates of blood flow the coronary resistance is greater than at high rates of blood flow, both in the control and lanatoside C periods. The resistance falls progressively as the coronary blood flow is increased, which suggests that the coronary vascular bed is a relatively passive one. Markedly reduced rates of blood flow were avoided in order to prevent deterioration of the preparation, so that a limited portion of the pressure-flow curve is available for analysis. In the flow range studied, most of the pressure-flow curves are relatively straight. Since lanatoside C increases the vascular resistance at all regions of the pressure-flow curves, they remain relatively straight during infusion of the drug.

The increase in resistance produced by this drug is, in part, dependent on the dose. In the experiments in which the drug was given intravenously, larger doses produced greater effects. In the experiments in which the drug was infused into the coronary perfusion circuit, the concentration of the drug infused at a constant rate was less at the higher rates of flow than at the lower rates of flow because of dilution. The drug-induced increase in resistance is somewhat less at the very high rates of blood flow. This may be due to the lower concentration of drug and therefore less vasoconstrictor stimulus. However, even a constant vasoconstrictor stimulus may be less effective when the intraluminal distending force is increased by the higher rate of blood flow.

The contradictory results reported in the literature are not easily explained. Unphysiologic preparations, variations in drug dosage, high concentrations of naturally occurring dilator substances, and inaccurate measurements of coronary artery flow may explain some disparate conclusions. This preparation has been found to be useful in studying coronary resistance because the heart is intact, beating, and performing work. It is subject to hormonal influences, and the nerve supply is disturbed only at the site of the left coronary ligature. The arterial blood is fully saturated with oxygen.[21] The disadvantages of anesthesia, an open-chest preparation, and altered coronary arterial phasic blood flow pattern produced by the pump do not invalidate the conclusions presented.

Summary

The effect of lanatoside C was studied in a preparation in which the flow of blood in the left main coronary artery could be accurately measured and varied. Lanatoside C produced an increase in left main coronary artery resistance at all rates of blood flow. The diluent of the drug did not affect coronary resistance. The increase in resistance persisted for the duration of the experiment. Some evidence is presented for a greater increase in resistance with larger doses.

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Detection of the magnetic field of the heart

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The electromotive forces of the heart set up currents in the torso which in turn produce magnetic fields. These fields are exceedingly small, having peak values less than one millionth of the strength of the earth field. Nevertheless, they may be detected, as is shown by the magnetocardiogram in Fig. 1.

This record was obtained using a specially designed assembly of two coils, each containing two million turns, and wound on a dumbbell-shaped core of magnetic material (ferrite) approximately a foot in length. The coils were oriented as shown in Fig. 2. The output voltage of these coils (of the order of 30 microvolts) was magnified by an amplifier of exceedingly low noise level and high input impedance and passed through a filter especially designed to suppress 60-cycle interference without significant distortion to the wave form of the signal. Because the coil is sensitive to the rate of change of magnetic field rather than the field itself, the record in Fig. 1 is actually a derivative of the magnetic field of the heart. It may easily be integrated to give the signal itself.

The record was obtained in an isolated location several dozen yards from the nearest source of interference. The ragged appearance of the baseline is due to noise generated in the coils and amplifier rather than to external disturbances. A program

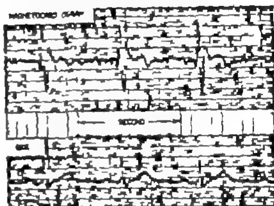


Fig. 1. Magnetocardiogram taken with coil placement shown in Fig. 2. An electrocardiogram taken simultaneously is also shown. The high noise level in the electrocardiogram is due to the long cable which extends to the subject.

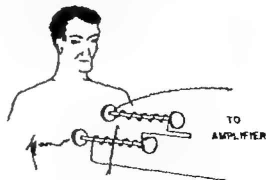


Fig. 2. Magnetocardiograph pick-up coils.

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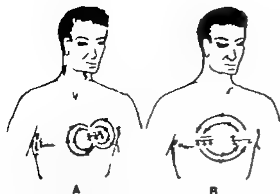


Fig 3 Flow lines of current within the torso giving rise to magnetic field. A Dipolar electromotive force. B Quadripolar electromotive force.

is now underway to design shielding which will permit the apparatus to be operated under normal laboratory conditions. Various improvements which will further reduce amplifier noise level are also being worked out.

The pickup assembly is extremely sensitive to vibration of the coil assembly in the earth field. To prevent this the coils are fastened to a heavy mount of great rigidity. Care is taken to see that vibrations are not transmitted to the coils from pulsations of the chest. Motion of magnetic material in the vicinity of the coils also gives rise to disturbances. A cancellation arrangement in which the output of two identical coils side by side are subtracted from each other gives considerable immunity to magnetic disturbances which do not arise in the immediate vicinity of the coils.

The magnitude and direction of the field is essentially the same as that predicted from the estimated distribution of current in the chest which must be associated with an electrical field in a volume conductor. It also agrees with measurements of magnetic fields made with a current dipole in a tank filled with saline solution which simulates the body.

This attempt to measure the magnetic field of the heart has been motivated by the hope that certain electrocardiographic anomalies will be more evident on such a record than on electrocardiographic records. The primary reason for this hypothesis is shown in Fig 3. In *A* of Fig 3 the flow lines of current which result from a dipolar electromotive force within the heart are sketched. Such a flow of current produces a tangentially oriented field on the chest over the heart. In *B* of Fig 3 the flow of current which results from a quadripolar combination of electromotive forces is shown. This current produces a magnetic field over the heart which is perpendicular to the chest. The electromotive forces in Fig 3,*B* are nearly silent in ordinary electrocardiographic records despite the fact that a strong circulating current is produced in and around the heart. Such currents will however set up detectable magnetic fields; thus, the magnetocardiograph offers the potentiality of detecting otherwise "silent" components of the electromotive forces of the heart. We have not as yet detected such circulating currents in normal subjects.

In normal subjects the magnetic field of the heart is maximum on the chest directly above the heart and dies away rapidly above, below and to the sides. At a point on the chest directly above the heart it is greatest in a direction tangential to the surface of the chest and oriented more or less toward the left arm. The component of the field at right angles to this direction is small. Differences exist from subject to subject.

Case reports

Primary reticulum cell sarcoma of the heart

Report of a case

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The purpose of this communication is to add another case of primary tumor of the heart to the list of previously reported cases and to emphasize certain aspects of the disorder. A complete review of the literature will not be attempted since excellent reviews have recently been published by several authors. Whorton re viewed 100 cases in 1949; Brucker and Glassy[4] reported an additional 43 cases in 1955, and Somers and Lothe[1] added 35 cases in 1960.

Primary tumors of the heart are quite rare. Straus and Merliss[18] estimated the necropsy incidence of both benign and malignant tumors of the heart to be about 0.0017 per cent. Somers and Lothe[14] found an incidence of 0.06 per cent of primary tumors of the heart in 6,644 consecutive autopsies. And Brucker and Glassy[4] found one case of primary malignant tumor of the heart in 11,131 autopsies performed at the Milwaukee General Hospital from January, 1928, to March, 1954. Only one primary malignancy of the heart was found in 1,537 autopsies performed at Wesley Hospital in Oklahoma City from 1945 to 1961.

Case report

A 40-year-old white male school superintendent who had previously been well was admitted to Wesley Hospital on July 15, 1961, and died 4 days later. Two months prior to admission he experienced cramping abdominal pain, and diarrhea which persisted for about a week. Approximately 1 month before admission he became aware of dyspnea on exertion and experienced mild episodes of nocturnal orthopnea. He thereupon consulted his local physician who hospitalized him and found that he was having fever. He was treated with antibiotics without apparent relief of his symptoms or his fever.

Physical examination. The temperature was 98°F., pulse 112 per minute, and blood pressure 102/46 mm. Hg. He did not appear to be acutely ill. The cardiac dullness extended 8 cm. to the left of the midline, and there was a diastolic gallop rhythm. There was no venous distention. The liver was not palpable and there was no peripheral edema.

Laboratory data. The hematocrit was 38 per cent, the hemoglobin 12.8 Gm. per cent. The white blood cells numbered 4,400 per cubic millimeter, of which 67 per cent were neutrophils, 17 per cent lymphocytes, 9 per cent monocytes, 6 per cent eosinophils, and 1 per cent basophils. The urine contained a trace of albumin and a rare hyaline cast. The V.D.R.L. was nonreactive, and the erythrocyte sedimentation rate (Wintrobe) was 22 mm. per hour. The serum transaminase was 26.5 mg. per cent. X-ray examination of the chest showed moderate generalized enlargement of the heart, and there were no pulmonary abnormalities (Fig. 1). The electrocardiogram revealed no significant QRS changes, but there was T-wave inversion in most of the precordial leads (Figs. 8 and 9). The patient had been digitalized prior to admission. The skin test with the intermediate P.P.D. was negative. The histoplasmin skin test was negative.

The temperature varied from 98 to 100.4°F. Four days after admission he suddenly became quite

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Fig 1 Ches -r film (posteroa terior iew) bowing gene lized enlargement of the heart Not lso the absence of ongestion in the l ngs.

dyspnea for few seconds nd then ceased breath ng became pulseless nd the heart tones were naudable The response to external cardiac massage was transient

A topsy findings.

GROSS The heart eighed 740 grams nd the myocardium throughout w pale gray yellow The epicardi m had finely granular ppearance. There ere several dense fibrous adhesions over the surfac most marked over the pulmonary artery nd left trium (Fig 2) The al es were normal. The myocardium as moder tely firm, except for several softened area scattered throughout the left entricle These are measured 2 t 4 mm i diameter and w re yellow They ere surrounded by 1 t 2 mm. of reddish discolored tissue (Fig 3). These were thought t represent mall bscesses in the myocardium The *only other significa t finding* wa the presence of several large, pale gray-yellow lymph nodes in the media tinum which measured 4 to 5 cm i diameter On cut section these howed area of focal necrosis.

MICROSCOPIC. The myocardium as diffusely in- olved by eticul m ell sarcoma. The sarcoma ells were fairly uniform with large round slightly hyperchromatic vesicula nuclei (Fig 5). Ma y of the cells contained prominent ucleoli, but mitotic figures were rare. The tumor cells p- peared to parallel nd separat the m scle fibers in many areas, whereas the muscle fibers themsel es appeared t be *relati ely normal* i the lesser in- vol ed areas. Ma y of the areas showed lmost com plete replacement of the myocardium by the tumor with only scant focal areas of myocardium remaining (Fig 4). Enlarged mediastinal lymph nodes were found adjacent t the heart but no other nodes ere i ol ed. Tumor cell were also found i the lungs and drenal gland especially around lymphatics nd blood essel The yellow patches noted grossly i the myocardium were focal rea of necrosis (Fig 6). A Wilder reticul'n tain on the myocardium revealed fine reticuli framework (Fig 7).

Comment Because of the exten n in ol ement of almost the entire myocardium with tumor cells nd the minimal focal nd dista t metastases, it was thought that the tumor as primary in the heart *ther tha in the medis tinal lymph nodes.*[14] This case i ery similar i its meta tatic pattern t 3 cases reported by Somers nd Lothe [14]



Fig 2 Photograph taken t utopsy of heart and lungs. Not adhesions over the pulmonary artery and left trium

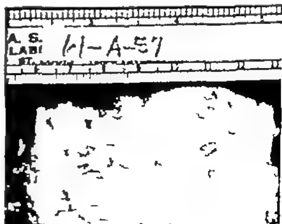


Fig 3 Photograph of the myocardium of the left entricle on cut section Not the small focal rea of necrosis.



Fig. 4. Low-power photomicrograph (×100) of the myocardium showing the diffuse pattern of the reticulum cell sarcoma with only scattered foci of muscle fibers remaining.



Fig. 6. Photomicrograph (×100) of the myocardium of the left ventricle to show area of necrosis (seen grossly, Fig. 3).

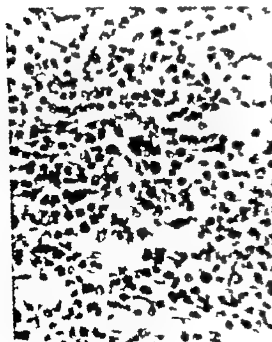


Fig. 5. High-power photomicrograph (×430) of the myocardium showing detailed structure of the malignant cells.



Fig. 7. Photomicrograph (×430) of the myocardium stained with Wilder reticulin stain, demonstrating the fine reticulin framework of the tumor.

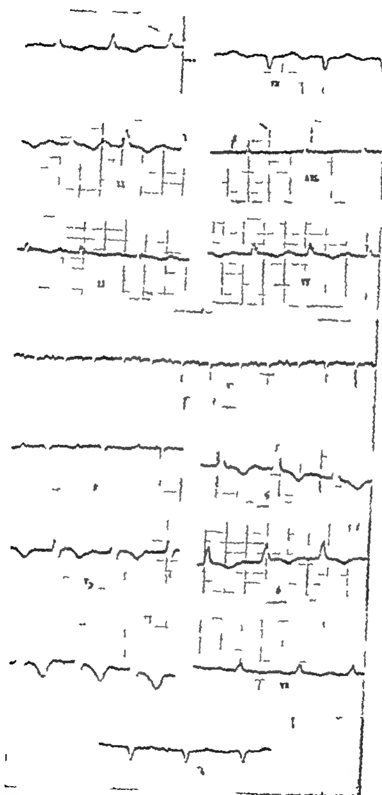


Fig 8 An ECG taken 2 day after admission of the patient to the hospital show primary T-wa changes left ventricular hypertrophy nd us tachycardia. Auricula r 105 entricula rat 105 QRS i terval, 0.10 sec P R interval, 0 16 sec ; Q-T interv l 0 36 sec T show inversion in Leads I II V2, nd V QRS transition occurs between Leads V nd V T show deep lat inversion in Leads V th ough V The intrinsicoid deflection in Lead V is 0 05 sec.

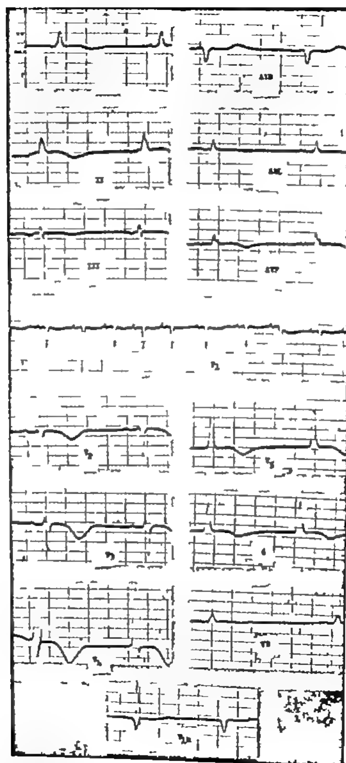


Fig. 9. A. ECG taken 4 days after admission of the patient to the hospital shows primary T changes, left ventricular hypertrophy, prolonged Q-T interval, an ectopic auricular pacemaker, runs of sinus tachycardia, and occasional auricular extrasystole. QRS interval, 0.10 sec. P-R interval, 0.12 sec. Q-T interval, 0.48 sec. P is inverted in Leads II, III, and V. T shows late inversion in Leads I, II, III, and V. Rate varies from 60 to 120 with slight configuration of the P waves. T shows late inversion in Leads V through V. QRS transition occurs in Lead V. The intrinsicoid deflection in Lead V is 0.05 sec.

Discussion

Boneti in 1700 and Morgagni in 1762 have both been credited with having been the first authors to describe primary tumors of the heart. However many pathologists believe that Albers reported the first authentic primary sarcoma of the heart a fibroma in 1835 Bodenheimer in 1865 described the first authentic primary sarcoma of the heart. This neoplasm was a spindle cell sarcoma that involved both auricles and originated in the right auricle.

As a rule tumors of the heart are not diagnosed clinically since they show no pathognomonic symptoms or signs. A few patients have died suddenly without previous warning of existing heart disease. In other cases the only clinical indication of a cardiac lesion was intractable heart failure without obvious cause. Very few cases have been diagnosed ante mortem. Shelburne[11] reported a case of spindle cell sarcoma in a 24-year-old man and listed his criteria for the clinical diagnosis of heart tumors.

Occasionally a primary tumor of the heart may take the form of a polypoid lesion that gives rise to a ball valve action on the tricuspid valve but this is more common with benign atrial polyps and atrial thrombi. Several syndromes are seen in association with tumors of the heart such as the superior mediastinal syndrome[12] and the so-called ball-valve syndrome. Even epileptiform attacks have been reported such as that due to a myxoma of the right atrium reported by Kendall and Symonds. Barnes Beaver and Snell[3] designated the electrocardiographic changes they believed to be important in making an antemortem diagnosis of tumor of the heart.

In 1955 Cooper and Hurst reviewed tumors of the heart particularly from a clinical viewpoint.

Primary malignant tumors may occur in any part of the heart but are the least frequent on a valve and most common in an atrium. They may be either single or multiple. Myxomas make up about 50 per cent of the primary tumors of the heart and 75 per cent of such tumors are located in the left atrium with symptoms occurring because of obstruction to the mitral valve.[4,5] This type of tumor is especially important since recent surgical developments may be lifesaving if the diagnosis is made early.

It is generally agreed that in all cases of tumor of the heart the neoplasm is of mesoblastic origin and therefore, it has been reported as myxoma fibroma lipoma lymphangioendothelioma hemangioendothelioma leiomyoma rhabdomyoma rhabdomyosarcoma leiomyosarcoma fibrosarcoma lymphosarcoma and polymorphous cell sarcoma. The exact classification of malignant heart tumors is impossible because of the variation in diagnostic criteria and histologic terms used by different authors particularly in the older reports.

The most frequent site of metastases is the lung. Other organs containing metastases are in order of frequency thoracic lymph nodes liver kidney pericardium adrenal glands and pancreas. In 100 cases reported by Whorton[7] the most common malignant tumor encountered was a certain type of spindle cell neoplasm including fibrosarcoma myxosarcoma fibromyxosarcoma and leiomyosarcoma. The next most frequent diagnosis was a variety of round cell tumor such as round cell sarcoma lymphosarcoma stem-cell lymphoma, and reticulum cell sarcoma.

In one series of cases the age of the patient at time of death ranged from 3 days to 79 years the median age was 43 years. Primary malignancies of the heart occur equally among men and women.

Summary

A case of primary reticulum cell sarcoma of the heart in a 40 year-old man is presented. The metastatic pattern of the tumor was similar to that of 3 cases previously reported.

We realize that one cannot categorically deny the possibility of origin of the tumor in the mediastinal lymph nodes with metastases to the myocardium but we believe that its origin in the heart was far more likely.

A brief discussion of primary heart tumors is given.

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Cor triloculare biatriatum

Report of a case with survival to the age of 29 years

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Cor triloculare biatriatum is an uncommonly encountered congenital heart defect. It is characterized by the presence of two atria and a common ventricle associated in 80 per cent of the cases with transposition of the great vessels.[1] Survival beyond childhood is rare and to date only 16 patients who were 21 years old or more have been reported. This paper presents the case of a seventeenth patient who survived beyond the age of 29 years.

Case report

A 29-year-old white woman was admitted to the Evangelical Deaconess Hospital on Nov 1 1961. The patient was 5 months pregnant and extremely short of breath. She was known to have had congenital heart disease and cyanosis since birth. Cardiac catheterization studies in 1954 had been suggestive of Eisenmenger complex. Her development was normal but her menstrual cycles were irregular and would occur only several times a year. When first seen by one of us (A. M.) in 1958 the patient had been taking digitalis for 4 years. Although very short of breath she was able to take care of her household and until 1956 had also worked in an office. On examination the pulse was [illegible] and regular the blood pressure was 150 75 mm Hg respirations were 12 and the vital capacity was 1 000 ml or 3 per cent of the predicted normal. The patient was cyanotic and her fingernails were clubbed. The ocular fundi revealed engorged venules and pulsating arterioles. The heart was markedly enlarged with the point of maximal impulse in the eighth left intercostal space in the posterior axillary lines. There was increased precordial activity and an intense systolic thrill was felt below the left breast and along the left sternal border. Grade 6 systolic and diastolic murmurs were heard along the left sternal border. Fluoroscopy showed marked generalized cardiac hypertrophy and the pulmonary vascular shadows were strikingly enlarged and pulsating. The electrocardiogram is shown in Fig 1 and the chest roentgenogram in Fig 2. The hemoglobin was 16.1 Gm per 100 ml. the red cell count was 7 6 million per cubic millimeter and the white cell count was 10 130 per cubic millimeter. Urinalysis was normal.

In December 1958 a cardiac catheterization study was carried out by Dr Henry Zimmerman. The findings are summarized in Table 1. All attempts to advance the catheter from a ventricular position into the pulmonary artery were interpreted as unsuccessful and resulted in getting into the apparent aorta. The difference of 5 volumes per cent in oxygen content between the right atrium and right ventricle indicated either a single ventricle or a very large interventricular septal defect, which would be the same physiologically as a single ventricle.

In November 1959 she developed increasing dyspnea and complained of dizziness palpitation

Table 1 Intracardiac catheterization studies

	Blood oxygen content (vol %)	Intravascular pressures (mm Hg)
Superior vena cava	12 80	
Right atrium	12 61	12/5
Right ventricle	17 74	120/12
Aorta	17 21	120 60

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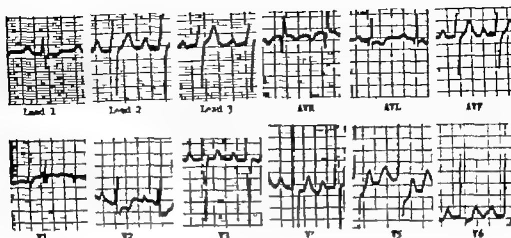


Fig. 1. Electrocardiogram showing first-degree A-V block, incomplete right bundle branch block, digitalis effect, and combined right and left atrial and ventricular hypertrophy.

nd grabbing sensation in the chest. She was omiting and her pulse rate had dropped to 40. An electrocardiogram showed 2:1 atrioventricular heart block. The digitalis was discontinued but the patient developed congestive heart failure and nodal tachycardia, and digitalis had to be given again. Episodes of 2:1 atrioventricular heart block and vomiting recurred. In March, 1960 because of a red cell count of 7.75 million per cubic millimeter, hemoglobin of 21 Gm. per 100 ml., and hematocrit of 67 per cent, two venesections were carried out and a total of 900 ml. of blood was removed. The vomiting ceased and the patient felt greatly improved. After the venesections the red cell count had fallen to 4.75 million per cubic millimeter, the hemoglobin to 17 Gm. per 100 ml., and the hematocrit to 45 per cent.

In May, 1961 the nausea and vomiting recurred and three more venesections were carried out, and an additional 1,300 ml. of blood was removed with good results. In order to avoid repeated venesections, 12 millicuries of radioactive phosphorus (P^{32}) were given in four divided doses between May 31, 1961 and July 3, 1961. On Nov. 1, 1961 the patient was seen because of extreme dyspnea, ankle edema of 1-week duration, and tightness in the throat and chest. The blood pressure was 152/0 mm. Hg, the pulse was 60, and the respirations were 42 per minute. The cardiac findings were unchanged and râles were present in the lung bases. The uterus was enlarged. The patient could not recall the date of her last menstrual period and had paid no attention to her amenorrhea because she had always had irregular periods. She was admitted to the hospital for the last time and upon arrival was too dyspneic to talk. She was seen by the consulting obstetrician and it was decided that therapeutic termination of pregnancy would give her the only chance of survival. It was quite apparent that she would succumb within a few days otherwise. On November 2, the membranes were ruptured with the patient practically sitting on the operating table. Several hours later she expelled a 7-ounce fetus. On Nov. 3, 1961 she became intensely cyanotic and apprehensive and died, 18 hours after the procedure.

Postmortem examination. On gross examination the body of this white woman was 61 inches in length and weighed 115 pounds. The conjunctiva and oral mucosa were pallid, the nail beds cyanotic



Fig. 2. Chest roentgenogram showing marked cardiac enlargement and prominent pulmonary artery.

Fig. 3. (1) ... dilated pulmonary artery. (2) ... pulmonary ... (3) Pocket behind ... septum. (4) Rudimentary septum.

the breast ... and both feet moderately edematous. There was ... clubbing of the nails. A small serous pericardial effusion (100 ml.) was present. The heart was firm and prominently enlarged ... the midaxillary line. It weighed 350 g. ... Diffuse ... fibrous ... found over the right ... epicardium.

The aorta rose to the right of and slightly ... the pulmonary artery. The venae cavae and pulmonary veins were normal in location and ... contained no lesions. The right atrium ... larger than the left. The atrioventricular ... were normally situated. The circumference of the ... small (9 cm.) and that of the mitral ... normal. These ... separated the ... from a large single ventricle which had ... 1.8 cm. thick ... measured 2 cm. below the atrioventricular sulcus, and ... 1.2 cm. ... the usual site of the pulmonary ... A ... shelf-like muscular ridge extended across the right anterolateral aspect of the ventricle perpendicular to its long ... It lay 5 cm. below the aortic ... and ... back to join the ventricular ... forming a pocket about ... 1.5 cm. deep (Fig. 3), situated ... of the aortic outflow tract (Fig. 4). This ... apparent rudimentary ventricle, the volume of ... one-tenth to one-twentieth of the volume of the single major ventricle. The aortic outflow tract had a diameter of only 15 mm. and the aortic ... measured 6 cm. in circumference compared to 10 cm. for the pulmonic ... One set of chordae tendineae of the tricuspid valve passed over the thick muscular ridge ... on the ventricular wall, confirming the belief that this ridge represented rudimentary interventricular septum. The aortic valve cusps were small. The three equal pulmonic valve cusps, each about ... the normal size, had a marked central fibrous thickening. The

circumference of the greatly dilated pulmonary artery was 14 to 15 cm. and the right and left branches were about twice the normal caliber. By contrast, the aorta was only 6 cm. in circumference ... similar ... Several thin atheromata were seen in the intima of the pulmonary artery and its right and left branches, and a series of alternating transverse ... ridges and depressions was seen in the intima 3 mm. from the pulmonic valve, forming lesions which measured 15 by 5 mm.

The coronary arteries arose in the aortic sinuses of ... and were distributed in the normal ... They contained no lesion. The major intrinsic branches of the pulmonary artery were markedly dilated and contained moderately numerous thin atheromata.

The uterus was in natural postgravid state. No further pertinent anatomic alterations were present.

Microscopic examination. The pertinent findings were limited to the lung. There was a fairly widespread disease of the pulmonary arteries and arterioles seen in many vessels in every section. A few of the largest arteries contained small atheromata. The arteries of medium and small caliber were diffusely affected by proliferation of fibrous connective tissue which caused prominent collagenous thickening of the intima and replacement of the media in sizable segments. Fairly often the small arteries and arterioles had thickened media due to muscular hypertrophy. Several small arteries and

Fig. 4. (1) Aorta. (2) Coronary artery ostium. (3) Rudimentary septum.

arterioles were occluded by old hypocellular fibrous connective tissue, and one organized canalized thrombus was seen in a small artery. In one small artery and one arteriole bits of mural thrombus were found, partially organized and focally covered by hyperplastic endothelial cells.

Discussion

In cor triloculare biatriatum survival into adult life is exceptional. In Abbott's analysis of 1,000 cases of congenital heart disease the condition occurred alone in only 13 instances. Her patients ranged in age from infancy to 35 years, the average lifespan being 7¾ years. Only 4 patients survived 21 years or more. Review of the literature reveals only 12 additional patients with survival to 21 years or more,[3-11] the oldest reaching the age of 56.

The condition apparently arises as a result of an extremely early arrest in the development of the heart. A single ventricle remains with, as a rule, a rudimentary outlet chamber representing the bulbus cordis.[12] Three types of cor triloculare biatriatum have been described.[13] In one type both the systemic and the pulmonary circulation arise from the outlet chamber. In the second type the aorta arises from the common ventricle and the pulmonary artery from the outlet chamber. In the third type the pulmonary artery arises from the ventricle and the aorta from the outlet chamber. The last is the most common and is associated with transposition of the vessels. In the case reported in this paper the latter situation existed.

Brown[14] stated that severe cyanosis is noted when the pulmonary artery arises from the outlet chamber. However, when it arises from the common ventricle the cyanosis tends to be less severe. This seems to be explained by the fact that the distribution of blood into the systemic and pulmonary circulations in the presence of a single ventricle is determined by the relative resistance offered to the flow of blood by these two circulations. Survival beyond an early age is rare because most of the flow of blood is directed into the pulmonary circulation, which is less resistant, thus letting a critically low flow of blood into the systemic circulation. When an increased resistance in the pulmonary circuit develops, some of the flow of blood is now diverted into the systemic circulation. In this way a more adequate volume of blood reaches the major organs of the body at the price of increased cyanosis. The increased resistance in the pulmonary circuit may be the result of a number of factors such as the site of origin of the pulmonary artery, decreased elasticity of that vessel due to atherosclerotic changes, and changes in the smaller pulmonary vessels manifested by hypertrophy of the media, intimal proliferation, and multiple intravascular thrombi. All these factors were present in this patient and probably were responsible for her reaching the age of 29 years and 11 months.

Summary

The case of a 29-year-old woman with cor triloculare biatriatum is reported. A discussion is presented of the possible factors that accounted for her survival into adult life despite a defect in which such survival is exceptionally rare.

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Fundamentals in vibrocardiography Precordial accelerography and acceleration ballistocardiography

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Precordial vibrations have a frequency range from 0 to 1,500 c.p.s. The greater part of these vibrations are audible as heart sounds and murmurs. They are recorded in phonocardiography. Only a small range of vibrations below 30 c.p.s. is infrasonic. The amplitude of these infrasonic vibrations is so much greater than that of sound vibrations that no filter is needed in their recording for excluding cardiac sound.

Infrasonic vibrations may be recorded as *displacement*, *velocity*, or *acceleration* of the thoracic wall. *Precordial displacement* plays an important part in cardiac diagnosis, because it forms a link between cardiac sound and hemodynamics.[39] Most of the transducers employed in vibrocardiography will give a flat response to acceleration when actuated by means of a vibrator, or they transmit the higher precordial frequencies only and give tracings which closely resemble an accelerogram. For this reason *vibrocardiography* has been more or less identified with *precordial accelerography*.[31-4]

Vibrocardiograms were shown to resemble acceleration ballistocardiograms,[39, 40, 41] but the initial systolic complex in vibrocardiography precedes the H J complex in acceleration ballistocardiography. This preceding of the ballistocardiographic acceleration complex was attributed by Hollis[4] to a "time lag" in ballistocardiographic recording.

There are some other resemblances as well between acceleration ballistocardiography and vibrocardiography. Just as in acceleration ballistocardiography, alterations were found in vibrocardiography with aging,[39] smoking, and induced anoxemia,[17] with weakening of cardiac muscle[17] and coronary occlusion.[16,17, 7] An abnormal reaction to exertion was found in angina pectoris.[17] Vibrocardiography was shown to indicate myocardial damage even before it could be found reflected in the electrocardiogram.[17, 7]

These various resemblances between acceleration ballistocardiography and vibrocardiography led to the suggestion of replacing acceleration ballistocardiography with precordial accelerography in order to circumvent the errors introduced into ballistocardiographic recording by limb impedance[16] and coupling of the patient to the ballistocardiographic bed.[16,3, 4]

Mounsey rejected this possibility be-

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cause of the influence of thoracic build and of the thickness of the intervening tissues on the vibrocardiographic pattern.[36] Hollis pointed out the difficulty of the absence of a mass value in translating precordial acceleration into "dynamic quantities of force." He also referred to the "problem of variability of wave form in different precordial locations, more so than can be accounted for by simple phase shift."[44] Nevertheless, some authors strongly recommended replacing acceleration ballistocardiography with vibrocardiography.[25]

A suggestion of this kind implies the possibility of acquiring the same kind of information with vibrocardiography as with acceleration ballistocardiography.

Acceleration ballistocardiography has been used in the estimation of stroke volume[illegible] and it has been related to cardiac "force."[illegible] It would seem necessary to test vibrocardiography as to this possibility of yielding a measure of stroke volume and of cardiac "force."

Exposition of the problem

Starr[illegible] states that "the amplitude of the ballistocardiogram is primarily related to the cardiac forces." In regard to stroke volume, he considers the relationship to be a limited one, "quite close when the ballistocardiogram is normal in form but when the ballistocardiogram is distorted the empirical formula giving best results when the flow is normal seriously underestimates the stroke volume."

It is evident that in cases of obstruction to the outflow, especially in aortic stenosis, there is no relationship of the ballistocardiogram to the cardiac forces at all. In regard to these estimations, ballistocardiography would seem to be of use in normal hearts only.

If it should be possible to determine cardiac "force" and stroke volume by means of precordial accelerography, this method might have the advantage of being useful in cardiac pathology as well.

It is necessary in this connection to realize exactly what precordial motion means.

If the heart were a stiff structure in which the "force" of ejection were generated in the same way as it is in a rifle, the reaction force to ejection transmitted to the thoracic wall might be comparable to cardiac "force," just as the repercussion of the rifle to the shoulder is comparable to the explosion causing the shot.

However, the heart is moved not only by repercussion, but it moves by itself even before ejection. During the whole of systole it heaves and presses against the thoracic wall, especially by means of the apex. Precordial movement certainly is more intricate than is the movement of the body as a whole under the influence of ejection.

Analyses of precordial tracings has been attempted by means of correlation with intraventricular pressure tracings obtained during catheterization. The initial systolic complex of the vibrocardiogram has been ascribed either to isometric contraction and the first thrust of ejection[illegible] or to isometric contraction alone.[illegible]

However accurate may be the determination of time relations between simultaneously recorded tracings, the fact that vibrocardiographic excursions coincide with intraventricular events does not prove them to be an expression of these events. Precordial acceleration is not acceleration in the rise of intraventricular pressure, nor yet is it acceleration of the heart moving on contraction. It is acceleration of the thoracic wall as it moves under the influence of ventricular contraction and emptying in systole, and ventricular filling in diastole.

The only way to interpret precordial acceleration correctly is by relating it to precordial displacement, of which it is the second derivative. The key to the question of the possibility of determining the "force" of cardiac contraction and stroke volume by means of precordial accelerography lies in the nature and the significance of precordial displacement.

Methods for recording precordial displacement and acceleration

Pulse tracings have been taken by means of a funnel or a tambour from the very beginning of registration on. The method was greatly improved by connecting the air tube with a crystal pickup. This combination was described for the first time in 1941 by Miller and White, who gave a detailed account of the frequency charac-

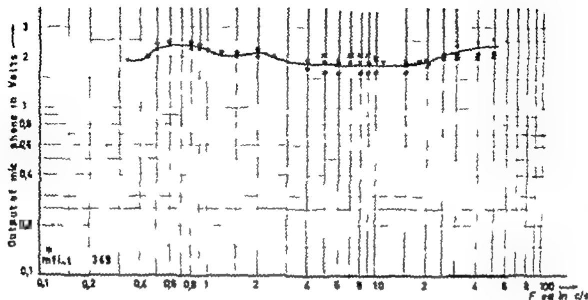


Fig. 1. Frequency response for constant displacement of the tambour connected to crystal pickup.

teristics of the pickup.[20] A year later Rappaport and Sprague[4] mentioned this method in connection with precordial vibrations and called it linear registration. Luisada and Magri[5] made use of it for taking precordial displacement tracings. It is the method employed by Holldack and Wolf[22] in their *Atlas und Kurzgefasstes Lehrbuch der Phonokardiographie*.

The Elongationsgeber developed by Schwarzer produces identical tracings and so does the displacement meter by Philips adapted to precordial registration by Schneider and Klunhaar.[23]

We used a tambour in connection with a crystal pickup manufactured by Hellige Works, Freiburg, Germany. The recorder was a four-channel photographic phonocardiograph by Hellige or by the Atlas Works, Bremen, Germany. It makes no difference whether a funnel or a tambour is used, because with the funnel the skin acts as a membrane. We prefer the tambour because with a closed system it is possible to examine the frequency response of the transducer as a whole. On actuation by means of a Goodman vibrator in which the amplitude was stabilized with reference to the displacement meter by Hottinger, the tambour in connection with the crystal pickup proved to give a flat response to displacement in the region concerned, i.e., from 0.3 to 50 c.p.s. (Fig. 1). The recorder has a flat response from 0.1 c.p.s. upward.

With the use of a funnel or tambour the movement recorded is with reference to the ribs on which the rim rests. The ribs and the intercostal space between them, the rim and the membrane, are all moved by the same impulse, but not to the same extent. The tracing is the result of subtraction, but it is not differentiated. We compared it with the tracing obtained by means of a photocell of the shadow thrown by a small cardboard rider attached to the skin. The photocell and the lamp were mounted in a unit which was attached to the patient's bed. The tracings obtained in this way give the actual movement of the thoracic wall which is not touched or influenced in any way.

The photocell was manufactured by Atlas Works, Bremen, Germany. The frequency response of this photocell in connection with the recorder proved to be flat to displacement from 0.1 to 150 c.p.s. on actuation by a vibrator.

A photocell of this kind would provide an ideal method for taking displacement tracings of the thoracic wall if the apex did not move during contraction and if a loose skin would not introduce disturbances of its own. The apex not only heaves during systole. It also moves upward and outward

Because of this movement the cardboard rider on the skin is inclined to tilt and waver With a loose skin as for instance under the left breast in women all kinds of secondary movements are introduced Even in men it is necessary to tighten the skin by stretching the right arm over the head Comparison then proved possible in young athletes with a somewhat broader apex beat. With the rider attached at the exact center of apical motion reliable and reproducible apexcardiograms were obtained which proved to be practically the same as the apexcardiograms obtained by means of the tambour (Fig 2) In a later paper a few slight differences will be discussed but for our present purpose they are of no consequence. It suffices to state that the apexcardiogram as obtained by means of the tambour proves to be a displacement tracing without any differentiation

In 1953 Hartman[3-6] at Leiden by means of the tambour method started correlating mechanography with phonocardiography as a routine procedure He took displacement tracings over the apex and the right cardiac thrust (if present) the carotid and femoral arteries the jugular vein and the liver and established the normal time relations with the phonocardiogram This pioneer work provided a firm basis for phonocardiographic interpretation. His method was adopted throughout the Netherlands. In regard to the apexcardiogram and the recordings of the right cardiac thrust his results were confirmed by a group of American workers[7] after one of them studied the method during a stay of 3 months in Utrecht in 1956

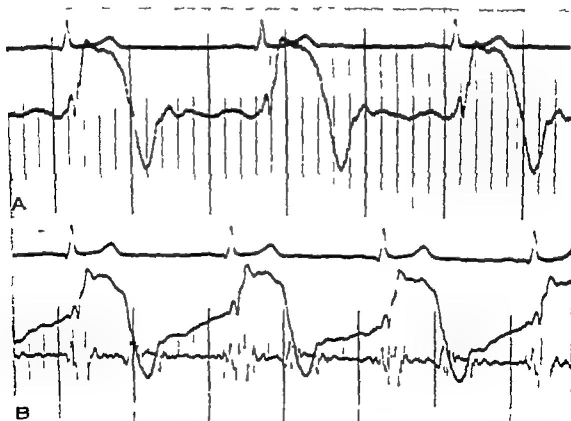


Fig 2. Comparison of apexcardiograms obtained with the subject in the left recumbent position as taken (A) by means of photocell and attached to the bed, from shadow thrown by cardboard rider attached to the skin over the apex, and (B) by means of the tambour During systole the two tracings are almost identical. In diastole the skin fails to reflect slow ventricular filling, which in the tambour tracing is seen as rising of the diastolic line.

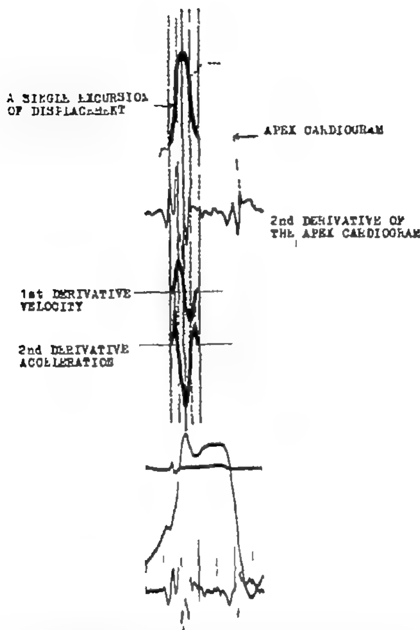


Fig 3 A single excursion of displacement considered as forming the petroke nd the beginning of the top of the pexcardiogram. Comparison of the celerogram which is derived theoretically from this single excursion of displacement with the second derivative of the pexcardiogram At the bottom are the ctual tracings from which the outline was taken for the comparison above.

Our own experience is based on complete phonocardiographic and mechanographic recordings in 3,300 cases, part of which were of normal people checked for sports competitions or of children with innocent murmurs. As for patients the clinical diagnosis was confirmed in the majority by right heart or left heart catheterization or both by operation or autopsy We added to the practice introduced by Hartman of recording both the apexcardiogram and an eventual right cardiac thrust by recording the movements over the zone of retraction movements low along the left sternal border and over the aortic and pulmonary orifice. These various tracings will be discussed separately farther on

Recording is done with the subject in

the left recumbent position in this position the contact of the heart with the thoracic wall is as close as possible and the cardiac movements are not influenced by gravity. It is necessary in recording the apexcardiogram to choose the exact position in which the systolic plateau is completely positive. Otherwise artefacts will be recorded, some examples of which Benchimol and associates reproduced. The nature of these artefacts will be discussed in the section on the zone of retraction.

We did not compare our results with those obtained by means of the method introduced by Eddleman nor with the tracings obtained with a new method by Bertin and Mounsey[illegible] since we lack experience with these methods.

In order to obtain an accelerogram at exactly the same place and at the same moment as the displacement tracing, the accelerogram was derived from it by means of double differentiation in the manner described by Burger and Noordergraaf for ballistocardiography.[illegible]

In the derivation of acceleration from displacement, however, a simple combination of resistances and capacitors proved to introduce a considerable disturbance due to hum and noise. For this reason operational amplifiers were used with an amplification of 30 000 and with frequency-dependent feedback. The amplifiers were stabilized in order to prevent drift. Cathode followers were used with the transducers in order to avoid hum at the input.

A few words on *the relationship between displacement and acceleration* may be of use in this connection. Acceleration may be derived from displacement either mathematically or on recording by means of differentiating electric filters.[illegible] The relation between a single excursion of displacement and its first and second derivatives (velocity and acceleration)[illegible] is shown in Fig. 3 (*heavily drawn lines*). In the ascending line of the single excursion of displacement there is a point at which the original concavity gives way to convexity. This point of greatest inflection marks the height of velocity. At the summit of the displacement tracing velocity is nil; here the velocity tracing crosses the zero line. The nadir of velocity is reached at the point of greatest inflection of the descending line in the displacement tracing. Velocity then returns to zero again.

Acceleration is derived from velocity in exactly the same way. As may be seen from Fig. 3, a single excursion of displacement is represented by a positive and a negative excursion of velocity and by a positive, a negative, and a second positive excursion of acceleration. The nadir of acceleration coincides with the summit of the displacement tracing.

The beginning of the systolic plateau in the apexcardiogram, its upstroke and the first thrust of ejection, may be considered to be a part of just such a single excursion of displacement. We shall refer to it again in the analysis of the apexcardiogram and the accelerogram derived from it by means of double differentiation.

Precordial displacement and precordial acceleration as derived from displacement: the relation to cardiac "force" and stroke volume

In an extensive study on precordial motion, Dressler[64] in 1933 pointed out the great difference between the movements of the exposed heart and those observed on the thoracic wall. The major movements of the exposed heart are in connection with cardiac filling and emptying. It is curious to see how little remains of these movements of filling and emptying on the thoracic wall. Here the chief movement is of the apex, which lifts as the heart contracts. In many cases it is the only movement which may be felt or seen.

In the normal heart the area taken up by the apex beat has, generally, a width of 1 inch or even less. In trained sportsmen, in thin and nervous people, in children after exertion and with emotion it may be broader. It is widened in cardiac overloading, and in severe hypertrophy the precordial surface as a whole may be heaving.

The apex beat in the normal heart of a subject in the left recumbent position is due to left ventricular contraction.[illegible] The right ventricle is no more than a rind over the frontal face of the much stronger cone-shaped left ventricle. Its border reaches the apex and moves with the left ventricular thrust. A small thrust of right ven

tricular origin may be observed along the left sternal border (Fig. 8,B). In right cardiac overloading it may be as forceful as the apex beat or even more so. In right ventricular hypertrophy and enlargement the left ventricle in many cases is forced away from the thoracic wall and then the apex beat itself is due to the right cardiac thrust. The following description of precordial displacement and acceleration over various areas of the precordial surface deals with normal movements.

1. *The apex displacement cardiogram and the apex accelerogram.* With the subject in the left recumbent position the apex is brought nearest to the thoracic wall and its movements are not influenced by gravity. In this position the systolic part of the apexcardiogram has the shape of a plateau with a descending top (Fig. 4,A). The upstroke starts 0.02 to 0.03 second after the beginning of ventricular activity in the electrocardiogram. Its summit marks the opening of the aortic valve. In Fig. 5,A it is shown to precede the carotid upstroke by 0.02 second. In many cases the crest of the upstroke is somewhat broader and either rounded or notched (Fig. 5,B and C). Whatever the form of its crest, the end of the straight upstroke always precedes the upstroke of the carotid artery by as much as the lag of the carotid artery, and this crest itself adds but slightly to the apical upstroke in a normal heart. The height of the upstroke in normal people is determined by the aortic opening, i.e., by diastolic aortic pressure.

With the first thrust of ejection the pressure of the apex against the thoracic wall decreases somewhat and because of this reduced apical pressure the plateau descends and is often more or less concave. The "force" of ejection maintains the elevation of the plateau but cardiac emptying causes it to decline. Only with muscular relaxation at the end of systole does the "force" which maintained elevation drop off. The plateau ends with a sharp downstroke which is less steep than the upstroke and reaches the deepest point, the dip, within 0.15 to 0.20 second. The dip coincides with mitral opening.* The diastolic line goes upward, since it is an expression of ventricular filling, of rapid filling during the remainder of ventricular relaxation, of slow filling after relaxation is accomplished, and of filling by atrial contraction.[3-7]

As for precordial acceleration, we are interested in the first systolic part of the apexcardiogram. It is this beginning of systole which is of consequence in acceleration because it is related to cardiac contraction and ejection. The downstroke of the apexcardiogram is related to ventricular relaxation only. A possible relationship between precordial acceleration and the "force" of cardiac contraction as well as its relationship to stroke volume must be searched for in this initial systolic complex of the precordial accelerogram.

Part of the single excursion of displacement described under a previous heading may be considered as constituting the beginning of the apexcardiogram, its upstroke and first peak (Fig. 3). In the apexcardiogram it is preceded by a small wave of atrial contraction. Generally, there is some overlapping of the final excursions due to atrial contraction and the initial excursions of ventricular systole in the acceleration pattern. With a large *a* wave the sharp transition between the *a* wave and the upstroke of the systolic plateau may by itself give rise to an excursion in the accelerogram. Moreover, every slight notch in the upstroke or in the first peak of the apex plateau may do the same. The simple pattern of the accelerogram as derived from a single excursion of displacement is overlaid by these fluctuations of various origin. For this reason the actual initial systolic acceleration pattern over the apex always is a more intricate structure than the theoretical accelerogram as derived from a single excursion of displacement. Yet something of the principle remains, as may be seen by a comparison of the theoretical and the actual acceleration patterns at the beginning of ventricular systole in Fig. 3. The descending line of the single excursion of displacement is not represented in the apexcardiogram. In its stead the line continues as the descending top of the apex plateau, thereby giving a more complicated sequel to the initial accelerographic excursions. The first peak of acceleration at the beginning of systole

*Part of these notches are the expression of cardiac sound.

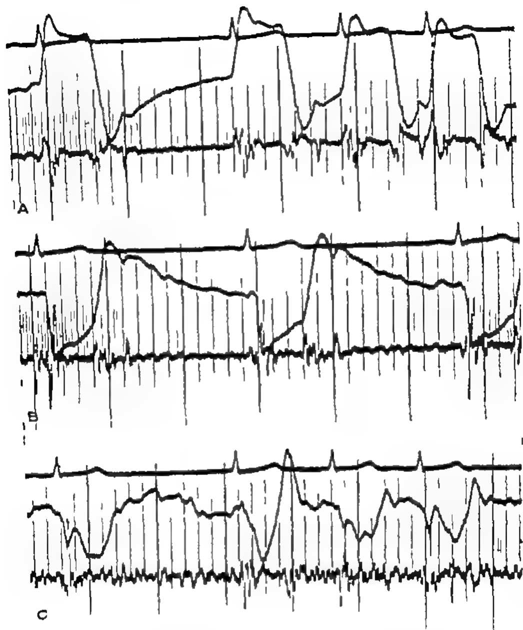


Fig. 4. Precordial displacement tracings with the accelerograms derived from them in a case of arrhythmia, with the subject in the left recumbent position. *A*, Apexcardiogram with accelerogram. *B*, Inverted apexcardiogram with accelerogram in the zone of retraction around the apex. Amplification 2.4 times the amplification of the apexcardiogram in *A*. *C*, Pulsations at 4L1 with accelerogram. Amplification 4.8 times the amplification of the apexcardiogram in *A*. The downstroke in *B* starts 0.04 second after the upstroke of the apexcardiogram in *A*, but otherwise the tracing is the exact reverse of the apexcardiogram. Not only is the systolic plateau inverted but the diastolic filling line as well. For this reason, the inward movement around the apex cannot be due to cardiac emptying alone. In *C* the displacement tracing in systole begins with a downward movement which in the smaller beats is broken by a positive wave. In the second beat after a long diastole the inward movement is deeper and the positive … has disappeared in this strong downward movement. The acceleration complexes are largest with the smaller beats where they coincide with the sharp transition from downward movement to positivity.

and its nadir which coincides with the summit of the upstroke may be recognized in many cases. They must always be present even though they may be deformed beyond recognition by incidental excursions due to minor irregularities of the displacement tracing. Every small notch in the apexcardiogram provided that it is sharp enough may give rise to relatively large excursions in the accelerogram because in the accelerographic excursions the square of frequency of the excursions in displacement is involved.

The nadir of acceleration at the beginning of systole coincides with the opening of the aortic valve or follows shortly after it. The acceleration pattern *precedes* this opening and *extends beyond it*. This means that the *first systolic acceleration complex over the apex is dependent on isometric contraction and on an interplay of the force of ejection and diminution of cardiac volume due to ventricular emptying. It is not related to cardiac force only. Consequently there is no possibility of estimating the force of cardiac contraction from the accelerographic amplitudes over the apex.*

The highest point in the normal apexcardiogram is reached at the summit of the upstroke. This summit is conditioned by the opening of the aortic valve (Fig. 5) which depends on diastolic aortic pressure and not on stroke volume. In a case of arrhythmia the apex plateaus in the consecutive beats proved to be of equal height although stroke volume certainly was considerably larger after a long diastole than after a short one (Fig. 4,*A*).

Since the height of the apexcardiogram depends on diastolic aortic pressure and not on stroke volume the accelerographic excursions over the apex at the beginning of systole afford no possibility of estimating stroke volume.

II. *The zone of retraction.* Around the apex there is a zone of retraction which has generally been ascribed to cardiac emptying[3, 8-22, 44] but tracings over this zone show a mirror image of the entire apexcardiogram. Not only is the systolic part inverted but the diastolic line with its distinct phases of rapid and slow filling and filling by atrial contraction is inverted as well (Figs. 4 *B*, 5 and 7,*A*, *C* and *D*).

Moreover this mirror image may be found to the left of the apex beat outside of any contact with the heart itself (Fig. 7 *C* and *D*) although less consistently and with smaller excursions.

Mirror images of this kind may be found likewise alongside of the arteries (see Figure 18a and b in the atlas of Holldack and Wolf[*]). A reaction of the soft tissues which are drawn in around any point which is pushed outward by pulsation may account for it. Whatever the explanation it is a feature in precordial registration which must be reckoned with.

At the transition zone between the apex and the zone of the mirror image composite tracings are found. The apex moves during contraction. In consequence of this movement the second half of the systolic plateau in the apexcardiogram becomes inverted if the tambour loses contact with the apex late in systole; a sharp inward movement at the beginning of the plateau may be caused by its gaining contact with the apex only after the systolic heaving has begun. The crest of the upstroke in systole and the dip and rapid filling in diastole would seem to be the last parts to resist the inversion in many cases (Fig. 6 *C* and *D*).

If the area of apical heaving is enlarged the mirror image may be found along the left sternal border (Fig. 7,*A*). In severe hypertrophy with heaving of the precordium as a whole the mirror image may be found over the right side of the thorax.

The zone of the mirror image of the apexcardiogram for obvious reasons is even less suitable than is the apex itself for the derivation of cardiac force or stroke volume from the accelerographic excursions.

III. *The zone of relative tranquility.* In most normal hearts there is a zone of relative tranquility beyond the zone of the mirror image especially in the third and fourth intercostal spaces along the left sternal border. Even in a normal heart a diminutive right cardiac thrust may be found somewhere within this zone especially in children (Fig. 8,*B*). It may be recognized by its having the shape of a plateau

$x = \sum A_k \sin 2\pi ft$

$\ddot{x} = -\sum_{k=1}^{\infty} 4\pi^2 f^2 \sin 2\pi ft$

but its height in recording generally amounts to a few millimeters, in contrast to an apex plateau of 50 mm In right ventricular hypertrophy it may attain the same dimensions as the apexcardiogram and the right ventricular thrust may dominate this region completely [3-8]

In a normal heart the right ventricular thrust if present is restricted to a small area In the remainder of the zone of tranquility a shallow inward deflection is found If this downward movement starts with isometric contraction as in Fig 8,*D* cardiac emptying alone cannot account for

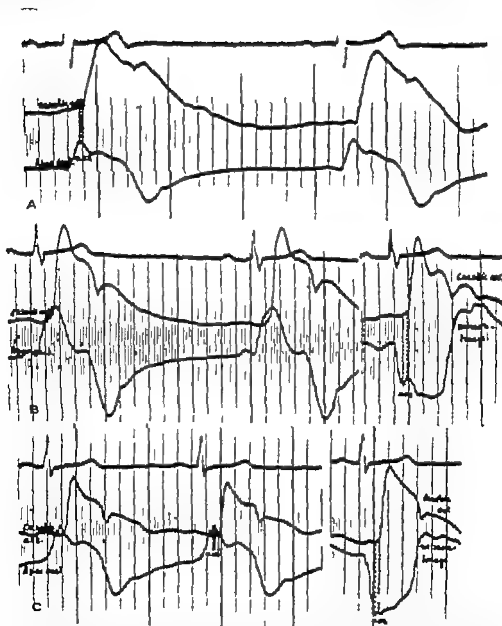


Fig 5 Three different shapes of the upstroke in normal precordiograms the summit of which may be sharp, as I A or somewhat broader and either rounded (*B*) or notched (*C*). In all instances the end of the straight upstroke precedes the carotid upstroke by as much as the carotid lag It height is conditioned by aortic opening If the broader crest surpasses the carotid upstroke as in *B* it hardly adds to the upstroke in the apexcardiogram of normal hearts.

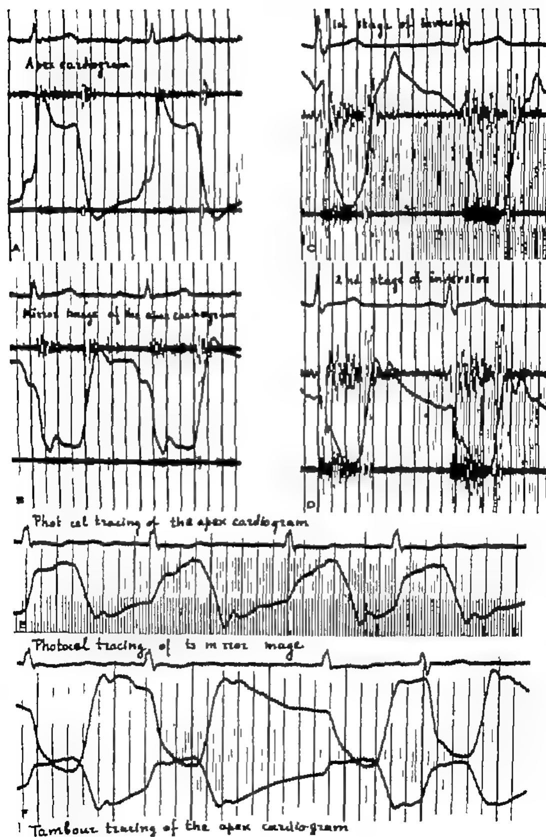


Fig. 4 (For legend see opposite page.)

it. Again the mirror image of the left or the right cardiac thrust may be of influence. Within this inward deflection a small positive wave is found which resembles the summit of the upstroke in the apexcardiogram or even its cut-off top (Fig 8,*A*). It may be due to a remnant of the left or right cardiac thrust which asserts itself within the inward deflection. It even may be due to the reaction force to cardiac ejection. In the latter case there might be some reason for comparing precordial acceleration at this point of predilection for vibrocardiography with acceleration in ballistocardiography. The sequence of negative deflection and positivity certainly creates a spurious resemblance to the pattern of the displacement ballistocardiogram which may account for the similarity between the vibrocardiogram taken at this point and the acceleration ballistocardiogram. Yet in ballistocardiography the negative excursion followed by a positive wave is due to the turning of the main stream of blood in the aortic arch which has no counterpart in precordial movement. The sequence of negative deflection and positivity on the thoracic wall arises from two movements which may change independently. This is borne out by Fig 4 *C*. In this case of arrhythmia the positive wave is seen best with the smaller beats after a short diastole in the first and fourth complexes. With the larger second beat after a long diastole the inward deflection is deeper and the positive wave has completely disappeared in its strong downward movement. If this positive wave is due to repercussion it certainly is not its unmitigated expression. The accelerographic excursions at the beginning of systole appear to be largest with the small first and fourth beats where they coincide with the sharp transition from downward movement to positivity. In the larger second beat this transition is absent and the accelerographic excursions are smaller.

In the zone of tranquility various contrasting movements are found which may change independently. The accelerographic excursions are favored by sudden transitions between these movements which bear no relationship to the "force" of contraction or to stroke volume.

IV. *The base of the heart.* Arterial pulsations may be recorded over the aortic or pulmonary orifices in cases of dilatation as for instance in the poststenotic dilatation of aortic or pulmonary stenosis. These pulse waves are of the arterial type. They start with ejection and in the downstroke an incisure is visible which coincides with the second aortic or pulmonary sound.

In right ventricular overloading and dilatation of the right ventricle the ventricular thrust may be recorded even in the second left intercostal space.

In a normal heart pulsations in this area are small—generally too small for recording. The distance from the thoracic wall is greater than over the heart itself and there is a considerable damping by lung tissues. The objections by Mounsey[16] and Hollis[8] to the use of precordial accelerograms for quantitation are more stringent yet as regards pulsations over the aortic and pulmonary orifices.

To conclude it must be stated that *no area of the precordium would seem to be suitable for the derivation of either stroke volume or the "force" of cardiac contraction from the accelerographic excursions.*

Fig 6 *A*. Apexcardiogram. *B*. Mirror image of the same apexcardiogram taken with 14/6 times its amplification. In systole the downward movement starts with isometric contraction. In diastole the filling line with its distinct phases of rapid and slow filling and filling by atrial contraction is inverted as well. Cardiac emptying alone cannot account for this mirror image, nor for the following ones. *C* and *D* are two stages of inversion in another case. In *C* the peak of rapid filling is still positive. In *D* the diastolic line as a whole is inverted. *E* is a photocell tracing of the apex movement in a third case. *F* is the mirror image of this apex movement taken by means of the photocell (*above*) with the simultaneously recorded tambour tracing of the apex movement (*below*). Amplification of the mirror image in *F* is 3 times the amplification of the apex cardiogram in *E*. These mirror images were all recorded over the right ventricle. During systole cardiac emptying tends to increase the downward movement of the mirror image but in diastole right ventricular filling is opposed to it. The downward line of the mirror image in diastole will show only if it can prevail over the influence of cardiac filling.

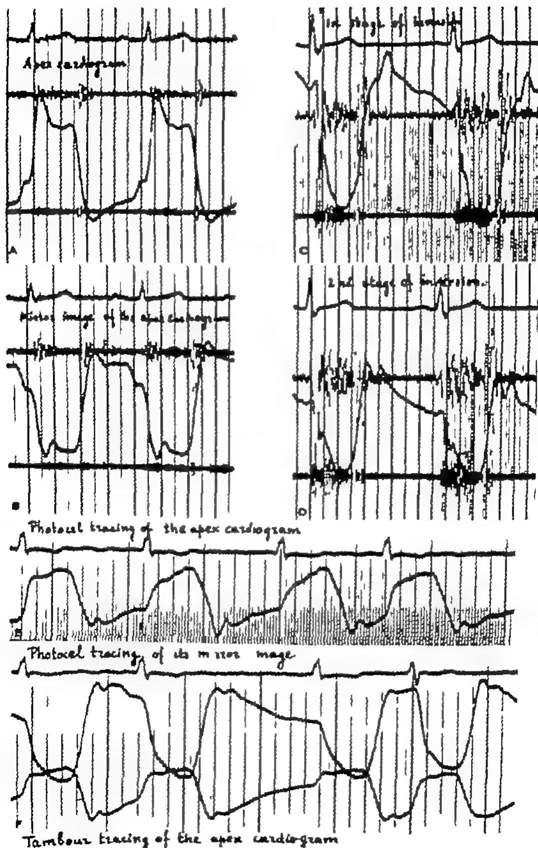


Fig. 6. (For legend see opposite page.)

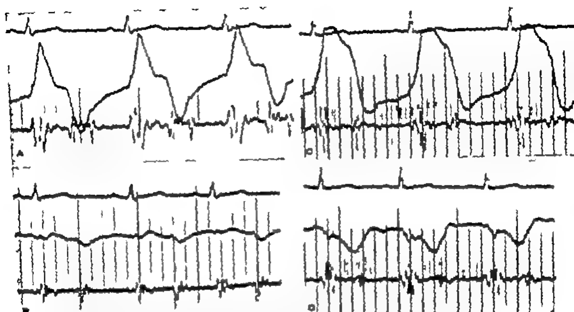


Fig. 8. Apexcardiogram (*A*) and small plateau at 4L1 of slight right ventricular thrust (*B*) in a normal heart. *C* is another apexcardiogram and *D* is the tracing at 4L1 in which downward movement starts with isometric contraction. Within this downward deflection a small positive wave is seen, the highest point of which coincides with the crest of the upstroke in the apexcardiogram. Constant amplification.

Comparison of the accelerographic amplitudes over the apex in mitral and aortic stenosis

In clinical practice, nevertheless, we are accustomed to estimate the "force" of cardiac contraction by means of palpation of the apex beat.

In order to clinch the matter beyond all possibility of doubt, we proceeded to derive accelerograms from apexcardiograms in widely different hemodynamic conditions. Two cases of severe mitral stenosis were compared with two cases of severe aortic stenosis. The four patients were in the same age group and of similar build. Amplification of the apexcardiograms was the same, and the relationship between the amplification of the apexcardiograms and the accelerograms derived from them also remained the same.

The four cases selected represented the following hemodynamic conditions: Case 1. *Severe mitral stenosis*—poor ventricular filling, low resistance to ejection (Fig. 9,*A*). Case 2. *Severe aortic stenosis*—small ventricular cavity, consequently poor ventricular filling, high resistance to ejection (Fig. 9,*B*). Case 3. *Severe mitral stenosis with some regurgitation and atrial fibrillation*—poor ventricular filling, low resistance to ejection (Fig. 9,*C*). Case 4. *Severe aortic stenosis and regurgitation*—ample ventricular filling, high resistance to ejection (Fig. 9,*D*).

Existing apexcardiograms were chosen for this investigation in order to include some cases in which the diagnosis had been confirmed by autopsy. For instance, in Case 2 (Fig. 9,*B*) the aortic aperture would allow passage of a knitting needle only

Fig. 7. *A*, Mirror image of the apexcardiogram taken at 5L1 with 3½ times the amplification of the apexcardiogram. *B*, Apexcardiogram at 5L9. *C*, Incomplete mirror image at 5L13 taken with 9 times the amplification of the apexcardiogram. *D*, Complete mirror image at 6L15 taken with 6 times the amplification of the apexcardiogram. *C* and *D* have been taken to the left of the apex, outside of any contact with the heart. Cardiac emptying cannot account for these mirror images.

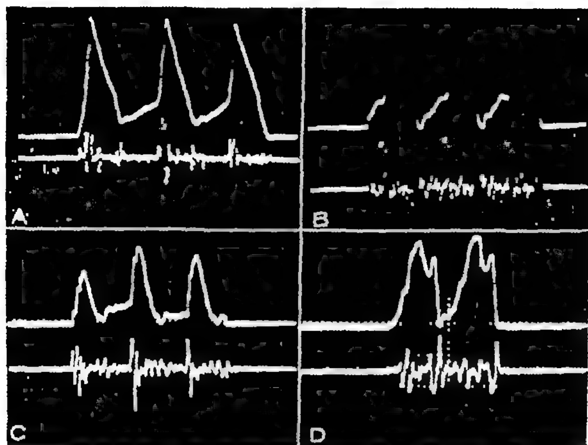


Fig. 9. Apexcardiograms and accelerograms derived from them in 4 patients in the same age group and of similar build. Constant amplification and constant relation in the amplification of displacement and acceleration. A, Mitral stenosis. B, Severe aortic stenosis. C, Mitral stenosis with some regurgitation and atrial fibrillation. D, Aortic stenosis and regurgitation.

but the mitral valve was proved to be intact. *The muscle of the left ventricle had a thickness of 5 cm.*

Method for obtaining accelerograms from existing apexcardiograms. An outline of the displacement tracing was cut out of cardboard and this silhouette was mounted on a disc which was rotated with uniform velocity by means of an electric motor. The shadow of this moving silhouette intercepted a varying quantity of light from a beam falling on a photoelectric cell. The electrical output of the photoelectric cell varies in the same manner as the shape of the original signal. These electrical variations are recorded by means of a cardioscope and the second derivative of this signal is recorded at the same time. The shape of the apexcardiograms reproduced in this way proved to be identical to the original tracings with the exception of the dip, which was less pronounced. For our purpose this was of no consequence since we were interested in the beginning of systole and not in the diastolic part of the apexcardiogram.

Results. In a comparison of the initial systolic acceleration complexes in these cases of mitral and aortic stenosis, the differences in the accelerographic amplitudes proved to be smaller than the differences in the height of the apex plateaus, especially in the beginning of systole. They certainly are not in the least comparable to the huge difference felt on palpation.[1] In the second case of severe aortic stenosis the

1. In estimating the "force" of cardiac contraction by means of palpation of the apex beat, we evidently take into account both the measure of heaving and its duration. At the University Clinic of Utrecht it is the custom to speak of "heaving" apex to indicate this long duration of heaving in ventricular hypertrophy. The duration of heaving, however, is not accounted for in accelerography.

greatest accelerographic excursions are related to the sharp downstroke after the late systolic crest of the apex plateau. At the beginning of systole the excursions would seem to be partly due to the large *a* wave and the sharp transition from this *a* wave to the ventricular upstroke. The part of the initial systolic acceleration complex due to ventricular activity may be smaller yet.

The reason for the failure of relationship between the accelerographic amplitudes and cardiac force may be explained in the following way. In mitral stenosis the steepness of the upstroke and the immediately following decline of the apex plateau involves a greater amount of acceleration and deceleration than does the slow sustained heaving of the apex in aortic stenosis. Even with a higher plateau the accelerographic excursions in aortic stenosis may be smaller than in mitral stenosis, and even smaller in relation to the height of the apexcardiogram than in a normal heart. This feature is borne out by the following experiment.

Comparison of a normal apexcardiogram and its second derivative with the apexcardiogram and accelerogram in aortic stenosis

In direct recordings of apexcardiograms and the accelerograms derived from them by means of double differentiation a fixed relation between the excursions of the apexcardiogram and of its second derivative had been obtained by using ganged potentiometers. Apexcardiograms brought up to the same dimensions by means of various degrees of amplification would give rise to accelerograms of more or less the same dimensions in normal hearts.

In Fig. 10 the upper record represents an apexcardiogram and accelerogram in a normal heart and the lower record represents those in a case of severe aortic stenosis with some regurgitation. The apex beat in aortic stenosis proved to be the stronger one. In order to obtain an apexcardiogram of more or less the same size twice the amplification was needed in the normal heart.

Result. This case of aortic stenosis is a special one because the *a* wave in the apexcardiogram is not large and angular as in most cases of aortic stenosis nor is there a sharp transition from the descending line of the *a* to the ventricular upstroke. The displacement tracing is rounded throughout. It is one of the few cases of aortic stenosis in which the initial systolic acceleration complex may be considered as representing ventricular activity without the disturbing aftermath of strong atrial activity overlaying its first excursions.

If the accelerographic amplitudes were related to cardiac force they should be greater in aortic stenosis. Since the two apexcardiograms were brought to the same dimensions the accelerograms likewise might have the same amplitudes. However the over-all dimensions of the accelerographic excursions in the lower record of aortic stenosis do not exceed 4 mm whereas in the upper record of the normal heart they amount to 40 mm. They are ten times as large in the normal heart as in the hypertrophic one with apexcardiograms brought up to the same size. Moreover they are smaller than normal in the hypertrophic heart as compared with the size of the apexcardiogram.

The reason for the exceedingly small accelerographic amplitudes in the hypertrophic heart can be found only in the absence of sharp transitions in the displacement tracing. The accelerographic excursions are related to the square of frequency of the excursions in displacement from which they are derived. The frequency content of the apexcardiogram proves to be of great consequence to the resulting accelerogram. Whenever the apexcardiogram is angular the accelerographic excursions are large. When the apexcardiogram is rounded as it tends to be in a hypertrophic heart the accelerographic amplitudes are small as compared with the acceleration pattern derived from a normal apexcardiogram of the same size.

Even the palpable difference between the force of the apex beat from a normal heart and the apex beat in ventricular hypertrophy and the difference between the tapping apex movement of mitral stenosis and the forceful thrust of aortic stenosis find no counterpart in greater accelerographic excursions with the stronger apex beat as might be expected if precordial acceleration were an expression of the force of contraction. The accelerographic excursion over the apex in left ven-

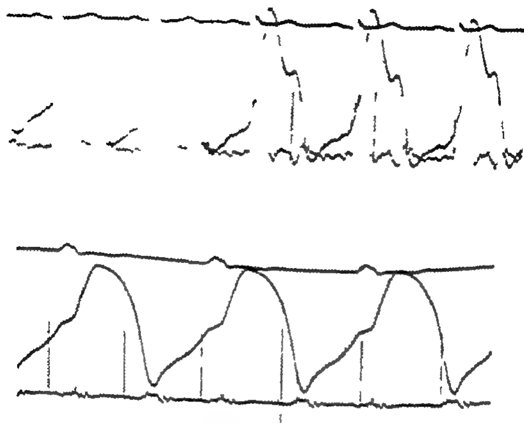


Fig. 11. Apex ... the left recumbent position. The ... were brought up to more or less the same dimensions by means of double ... normal person and the lower ... with severe ... Constant relation in the ... of displacement ...

... hypertrophy even tend to be smaller than the normal ones because of the rounding of the apexcardiogram which is a constant feature in systolic overloading.

Conclusion

The inaccuracies of acceleration ballistocardiography have led to the suggestion of recording precordial acceleration instead. The estimation of stroke volume and of cardiac force by means of precordial accelerography, however, proves to be impossible.

In the case of myocardial damage small amplitudes have been observed in both acceleration ballistocardiography and vibrocardiography. Small amplitudes in precordial acceleration may be caused by ventricular hypertrophy as well as by myocardial damage. The place of predilection for taking vibrocardiograms, low along the left sternal border, is by no means exempt from the influence of ventricular hypertrophy, either from left or from right cardiac origin. Further investigation will be needed in order to establish a possible difference between the acceleration pattern of ventricular hypertrophy and that of myocardial damage.

In any case it would seem advisable to always register a displacement tracing with the accelerogram. The possibility of the simultaneous recording of them at the same place on the precordium is ensured by deriving the accelerogram from displacement by means of double differentiation.

Summary

Most transducers employed in vibrocardiography give a flat response to acceleration when actuated by means of a vibrator or they record only the higher precordial frequencies and give tracings which closely *resemble* an accelerogram. For this reason vibrocardiography has been more or less identified with precordial accelerography. Moreover the vibrocardiographic pattern resembles the pattern of acceleration ballistocardiography. The replacement of acceleration ballistocardiography by vibrocardiography has been suggested as a means of avoiding some of the errors introduced into ballistocardiography by limb impedance and by coupling of the patient to the ballistocardiographic bed.

Acceleration ballistocardiography has been used for estimating stroke volume and it has been related to cardiac "force." Precordial accelerography was tested with regard to the possibility of estimating both with greater accuracy. In order to do so the precordial accelerogram was compared with the precordial displacement tracing of which it is the second derivative.

The initial systolic acceleration complex starts with isometric contraction and continues during the first thrust of ejection. Heaving of the thoracic wall on ventricular contraction and its deflection caused by cardiac emptying are both involved in it. So are movements of the precordial soft tissues, which are drawn in around the apex as the tissues over the apex itself are pushed outward. This complexity of precordial movements precludes the possibility of considering precordial acceleration as a measure of the "force" of cardiac contraction.

Moreover, the accelerographic amplitudes are favored by sudden changes in the direction of precordial movement, which are more likely to occur in the case of poor ventricular filling and low resistance to ejection than in cardiac overloading. This is but another aspect of the same complexity of precordial motion which demonstrates the impossibility of using precordial acceleration as a measure of cardiac "force."

The highest point in the normal apex cardiogram is reached at the summit of the upstroke. The height of the upstroke is conditioned by diastolic aortic pressure and not by stroke volume. In a case of arrhythmia the apex plateaus proved to be of equal height, although stroke volume certainly was larger after a long diastole. If stroke volume is not represented in displacement, it cannot be derived from its second derivative either.

Inasmuch as the purpose of acceleration ballistocardiography is the estimation of stroke volume and of cardiac "force," precordial accelerography cannot replace it.

Small amplitudes in vibrocardiography, moreover, are not a proof of myocardial damage. They may indicate ventricular hypertrophy. Along the left sternal border a strong right cardiac thrust may give rise to an abnormal vibrocardiographic pattern.* Comparison of vibrocardiographic recordings with the simultaneously recorded displacement tracings over the same precordial area would seem imperative.

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*In Fig. 4 of a recent publication by Ross and associates,[11] this is clearly the case. Within the accelerographic pattern ... of the ictus plateau is seen. This feature in vibrocardiography is found ... strong cardiac thrust either from left or from right cardiac areas.

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Fundamentals of clinical cardiology

Idiopathic pulmonary hypertension

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The pulmonary circulation has undergone intensive study since 1553 when Servetus, at the cost of his life published *Christianismi Restitutio* and in it an accurate description of the pulmonary circulation Many great figures will suggest themselves when while paying tribute to the lucidity of his observations we consider the advances which have followed While it is fascinating to wonder how such men would set about the solution of problems like atheroma and hypertension we are reminded that hypertension in its various aspects remains a problem to the scientist and to the clinician. This is as true of idiopathic pulmonary hypertension as of essential hypertension

Idiopathic sometimes called primary pulmonary hypertension or neatly by Evans, solitary" pulmonary hypertension is listed in a special category of Wood's classification since obliterative lesions or reactive vasoconstriction according to this classification may be involved although the former are most always to be found at autopsy There must be no evidence of a large single communication between the two circulations but absolute proof of this must in the present state of knowledge await autopsy These obliterative changes include thrombosis, intimal hyperplasia and arteritis-like lesions, the result of necrosis such as occurs in many small vessels in malignant hypertension and not unlike the lesions in small systemic arteries in polyarteritis nodosa. Secondary muscular hypertrophy may occur in medium-sized arteries, and indeed muscle tissue may appear in arteries of a size which in adult life do not contain muscle Furthermore vasoconstrictive changes may in turn follow obstructive lesions, but in some instances it would appear that increased vascular tone has been the initiating lesion

Idiopathic pulmonary hypertension as usually described occurs in young women between the ages of 20 and 40 but patients of both sexes and at most ages have been reported in the literature.

Symptoms are usually effort syncope, weakness and cardiac pain but breathlessness and cough with or without hemoptysis may occur Cyanosis is frequently present but careful observation reveals that it is often peripheral. Although clubbing of the fingers is rare evidence that the cyanosis is sometimes central is supplied by Kuida and associates, who reported polycythemia in 3 patients, a fact of considerable importance when we try to interpret the pathologic findings.

The relationship of infection to idiopathic pulmonary hypertension is uncertain but a febrile illness occurs sometimes in the early histories of many of the patients, with a variable period of health between the fever and the onset of the pulmonary hypertension [4] It is difficult therefore to ignore infection as a possible

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etiological factor. The onset otherwise may be insidious, and usually death occurs within 1 to 3 years after the onset of symptoms, the more rapid progress of the disease being observed in the younger patients.

Of particular significance may be the observation that many of the patients have suffered in the past from Raynaud's disease or from arthritis or from lesions suggestive of connective tissue disease.

The diagnosis from physical examination is suspected by the characteristics of pulmonary hypertension without an obvious cause such as lung disease, mitral valve disease, or a congenital cardiac malformation. Great care must be taken to exclude recurrent embolism from a peripheral venous thrombosis of unknown site or such as may result from injury or from pelvic trauma which is the result of operation or pregnancy.[4] A rare cause of pulmonary hypertension that is difficult to recognize is congenital stenosis of the pulmonary veins as described by Reye[23] and more recently by Shone and associates,[25] who advise selective angiography to aid diagnosis.

The signs are a giant "a" wave in the jugular venous pulse, more readily observed in adults, palpable right ventricular overactivity, and a loud sound of pulmonary valve closure succeeded or not by a pulmonary diastolic murmur. In those patients in whom right ventricular failure occurs it is usual to hear the pansystolic murmur of tricuspid regurgitation.

Serial electrocardiography reveals right ventricular hypertrophy of a progressive nature, and a tracing taken after standard exercise may suggest ischemia by depression of the S-T segment. Radiograms show some cardiac enlargement, particularly of the right atrium, enlargement of the pulmonary artery and proximal branches, and ischemic peripheral lung fields.

In patients whose lung function has been studied the results are normal.[14] Cardiac catheterization supports the diagnosis by revealing pulmonary hypertension of considerable or severe degree and no evidence of left-to-right or right-to-left shunt. But, in addition, it may afford an opportunity to test drugs whose efficacy has been suggested by experimental work. The frequent inability to obtain left atrial pressures after attempts to wedge the catheter may indicate a sudden change in the caliber of vessels. But it may mean that certain new formations of vessels referred to below vitiate the true wedge readings by transmitting pulmonary arterial pressure via abnormal channels to the tip of the catheter.[19]

Postmortem arteriography, as practised by Doyle and associates and Evans and associates, reveals extensive reduction or obliteration of the lumina of the small pulmonary arteries and confirms the impression gained from the routine chest films of ischemic peripheral lung fields, upper and lower zones of the lung being equally affected, unlike the lungs of patients with mitral stenosis.

Much information is to be gained from a study of histologic preparations of lung tissue, but the interpretation of the origin of the changes which are observed is not unanimous. It should be noticed that Dresdale[1] has reported normal histologic appearance of lungs at autopsy in patients who died from idiopathic pulmonary hypertension. Nevertheless, in most instances structural changes are to be found ranging from minimal hypertrophy of the media of muscular vessels to vascular necrosis and organization. Between these extremes are found intimal hyperplasia and thrombosis, both recent and organized. Sometimes thrombosis may appear to be related to vascular damage, but at other times no certain vascular lesion is observed in the plane of section, although such can be found in serial sections. Muscle tissue may appear in small arterioles under 100 microns in diameter in which it is not normally found after infancy. Difficulty in the interpretation of cellular thickening of the internal regions of a vessel frequently leaves doubt about whether this represents true intimal thickening or organizing thrombosis. Intimal thickening will usually involve the whole circumference of a vessel wall, whereas organizing thrombosis may be represented by eccentric cellular tissue with or without obvious damage to the underlying medial layers. Occasionally internal cellular thickening represents longitudinally arranged muscle fibers.[3]

Considerable attention has been given to defective portions of the media observed by many authors, areas in which there appears to be compensatory intimal thickening. Evans suggested that the areas represented congenital deficiencies of the media, and James remarks that the intimal reaction may well be compensatory for the medial inadequacies but is uncertain whether the medial lesion is congenital or acquired. It is true, however, that similar atrophic areas of media may frequently be observed external to organizing acquired thrombosis in a muscular vessel.

Because of the occasional observation of central cyanosis in some patients, there has been a search for communications between the bronchial arteries and the pulmonary arteries and between the pulmonary arteries and veins. New formations of vessels have been observed and referred to by Wagenvoort simply as abnormal vascular formations, or by Naeye and Vennart as plexiform structures. Because of their varying appearance Heath has classified them as plexiform lesions, vein-like branches of muscular pulmonary arteries, angiomatoid lesions, and cavernous lesions. The plexiform structures, so Naeye and Vennart believe, may represent recanalized thrombi. They could not demonstrate any abnormal communication of pulmonary and bronchial vessels. Wagenvoort, who after meticulous histologic examination described thin-walled vascular clusters in cases of severe pulmonary hypertension, believed that they did not represent bronchopulmonary anastomoses, and states that in the sections which he examined the abnormal formations of vessels could be traced to pulmonary capillaries. If central cyanosis occurs in certain patients with idiopathic pulmonary hypertension, it has been thought to indicate either the opening of a foramen ovale or perhaps interstitial thickening of the pulmonary parenchyma, such as has been observed by Goodale and Thomas, by Tomatsu and associates, or even increased cellularity of alveolar walls as reported by Kuida and associates. However, some interstitial thickening need not deny the diagnosis of idiopathic pulmonary hypertension although, as previously mentioned, such is seldom sufficient to produce obvious impairment of other lung functions. Kuida along with Naeye and Vennart and Wagenvoort states that unusual vascular channels were ultimately traced to alveolar capillaries. Shepherd and associates agree with Naeye and Vennart that plexiform structures represent healed and organized thrombotic lesions. On the other hand, in a report on 10 patients with idiopathic pulmonary hypertension Wade and Ball demonstrated bronchopulmonary anastomoses in 2 of them, and Evans[1] observed abnormal bronchopulmonary anastomoses in idiopathic pulmonary hypertension. Brewer and Heath have demonstrated bronchopulmonary anastomoses in the Eisenmenger syndrome.

Since experimentally[17-19] bronchial vessels in the lung develop in response to the blocking of a pulmonary artery and distal to it, if this is a mechanism in idiopathic pulmonary hypertension, it would seem unlikely that the reversal of blood flow in such abnormal vessels could occur and so be responsible for central cyanosis. Liebow has suggested that because the blood from bronchial veins may run either to the left or to the right atrium, a rise in filling pressure of the right ventricle, such as would occur in severe pulmonary hypertension, might direct more unsaturated blood into the left atrium, and this would appear to be a very reasonable explanation of cyanosis in certain patients with primary pulmonary hypertension in whom there is no single large communication between the pulmonary and systemic circulations.

Vascular necrosis has frequently been observed, but the distinction histologically from polyarteritis affecting lung vessels is difficult. Rose and Spencer examined the records of 104 patients with polyarteritis nodosa and separated them into two groups—those with lung involvement and those without lung involvement. They found that characteristics of the disease in each group were distinct, although they had excluded from their study 2 patients with polyarteritis-like lesions in the lung alone associated with pulmonary hypertension since they assumed that the pulmonary hypertension had preceded the arteritis-like lesions. It would appear from their descriptions and from other

studies that polyarteritis nodosa in which the lungs are involved as part of a more general picture is a different disease from that in which lesions are found in lung arteries alone. Harrison[14] states that in his experience polyarteritis nodosa involves lung vessels in a minority of instances only and that in such instances the lesions do not contribute significantly to pulmonary hypertension

Necrosis may indicate the rapidity and severity of pulmonary hypertension In an autopsy described by Reye[25] the patient a 4 year-old Mongol female child had undergone repair of an atrial septal defect. An unsuspected 2-cm ventricular septal defect was found at autopsy Histologic sections of lung revealed many areas in which small pulmonary arteries had become necrotic and infiltrated with inflammatory cells the lesions resembled those seen in the systemic circulation in rapidly progressive severe hypertension The hemodynamics of this unusual situation are difficult to explain but it may be significant that before operation the pulmonary artery systolic pressure had been lower than the systemic by some 30 to 40 mm. Hg Patients with large ventricular septal defects alone do not uniformly have equivalent pulmonary and systemic arterial pressures, as demonstrated by Lynfield and associates.[26] In the instance described, extra blood which would have entered the left ventricle after operation could have been shunted via the ventricular septal defect at systemic pressure levels, thus suddenly raising pulmonary arterial pressure

The findings of involvement of systemic vessels in reports[4, 8, 9] of otherwise acceptable instances of idiopathic pulmonary hypertension may be particularly significant. The systemic lesions were similar to those found in pulmonary arteries of similar size. It appears that in each instance it was the obstruction produced in the pulmonary circulation which was the cause of death and that the systemic involvement had not contributed directly to death Particular attention was paid by James to that branch of the right coronary artery which supplied blood to the sinoatrial node and he implicated its involvement as a possible cause of arrhythmia and syncope to which these patients are prone.[17] The pulmonary vascular lesion was believed to be part of a generalized degeneration of the media accompanied by thickening of the intima in small arteries, especially pulmonary coronary and adrenal arteries but with its most devastating effect in the lung

When it is shown that lung vessels are more severely affected in a generalized arterial disease, immunologic reactions must be considered and their variable effects in different tissues An immunologic basis for idiopathic pulmonary hypertension has not been shown but there are some suggestive facts. In 1932 Grove[3] produced an anaphylactic reaction in the rabbit which resulted in pulmonary vasoconstriction and although systemic vasoconstriction was also produced death was due to right ventricular failure This kind of anaphylactic reaction does not necessarily apply to other experimental animals.

One is tempted to draw an analogy between certain collagen diseases and idiopathic pulmonary hypertension because of the effect of both groups predominantly in women of similar ages. Furthermore Wade and Ball[29] found a positive differential agglutination test in 3 of the 10 patients with idiopathic pulmonary hypertension on whom they reported

Raynaud's disease although not classed as a collagen disease is one in which the initial stages are characterized by increased vascular tone in the hands, and later by structural vascular change and it affects predominantly a similar age group and the same sex as does idiopathic pulmonary hypertension The mention of Raynaud's disease in the histories of many of the patients so far reported on is also striking Of especial significance may be the occurrence of Hashimoto's disease in a patient reported by Rawson and Woake

The medial degeneration and deficiency referred to by Evans and noticed by other authors and suggested as being of congenital origin as mentioned previously may well be an acquired degeneration rather than a congenital one

A clearly antigenic reaction has been produced in the lungs of the rat by Read[27] who instilled rabbit anti-rat lung serum into the

respiratory passages. Sections of these lungs did not in any way resemble those from human beings with idiopathic pulmonary hypertension but the antigenic serum did not come into direct contact with vessels. The first muscular arteries encountered by an antigenic stimulus circulating from the peripheral systemic circulation would be those in the lung

The medial hypertrophy of muscular vessels referred to by most authors who have studied histologic sections are thought by some to represent a persistence of the muscular type of small arteries and arterioles which are found in the fetus.[illegible]

Whether idiopathic pulmonary hypertension is a congenital or acquired disease is of first importance when one attempts to discover its cause A consideration of the careful work of Heath[illegible] presages much help in answering this question He pointed to the similarity of histologic appearances in the aorta and main trunk of the pulmonary artery in the fetus and indicated that this was so because of the similar stresses to which each vessel is subjected in intrauterine life The precipitous fall in pulmonary vascular resistance at birth now thought to be due to a fall in vascular tone[illegible] rather than to the straightening of contorted blood vessels is followed over a period of 3 to 6 months by a more gradual fall This is occasioned by an atrophy of the intima and media of small vessels whose thickness strength and reactivity are no longer required in the adult circulation Furthermore atrophic changes occur also in the right ventricle and in the main pulmonary vessels most strikingly observed by examination of the media of the main trunk of the pulmonary artery when stained for elastic tissue The closely packed and parallel nature of the elastic fibers is replaced by shorter more irregular fragments which have thickened rounded ends, surrounded by increasing amounts of collagen Heath postulated that once the atrophic change has taken place, should the vessel wall then be subjected to increased pressure from within this atrophic adult pattern would remain On the other hand if the high flow which lead to high pressure had been maintained since birth as for example in the case of a large ventricular septal defect the fetal pattern was retained Examination by Heath in several instances of pulmonary hypertension of differing etiologies appeared to confirm his idea although it implied a certain inability of elastic tissue in the pulmonary artery to regenerate under circumstances of increased pressure.

Examination of the main trunk of the pulmonary artery by Heath's technique applied to children with idiopathic pulmonary hypertension did not support Heath's theory unequivocally in that they appeared to have an intermediate pattern But when compared with a true Eisenmenger ventricular septal defect in which high pressures had been present since birth their parallel closely packed fibers presented a distinctly different pattern And the difference was equally true in the boy and two girls. Having seen sections from one of the girls Harrison[illegible] had no doubt that this confirmed the acquired nature of the disease. Heath himself[illegible] having seen only the section from the boy stated that this was one of only two instances in which he had been unable to state categorically the congenital or acquired nature of the disease and wondered whether it applied only to male patients, as indeed he had suggested elsewhere.[1] But the pattern in the young girl was similar[8] Since the Heath technique has otherwise been found to be so reliable, the evidence in these patients supports the belief of the acquired nature of the disease because the pattern in these patients was so very different from that found in the Eisenmenger group

Heath's theory could be more accurately tested by estimation by the hydroxyproline technique of the elastin and collagen content of vessels of the pulmonary circulation which have also been subjected to histologic examination Although this might appear to be a troublesome way of confirming the histologic appearance it may be possible to correlate the findings with physical characteristics of the vessel for example pulse wave velocity The same has been measured in the rabbit by Caro and McDonald[illegible]

If it can be firmly established that idiopathic pulmonary hypertension is an acquired disease then investigation of possible immune origins might be undertaken

with greater confidence. This would be a formidable task, but there has been experimental work to suggest it as a reasonable possibility. Following the work of Grove, Halmagyi[39] has produced in sheep a syndrome of pulmonary hypertension with pulmonary arteriolar constriction and terminal airway closure after transfusion of incompatible blood and staphylococcal endotoxin. It must be made clear that any relationship between this acute anaphylactic reaction in sheep and pulmonary hypertension in human beings is not established. The proposal of an immune reaction as a cause of idiopathic pulmonary hypertension would suggest that the primary lesion is a vasospasticity and that all changes reported in various instances followed from high pressure so induced. The varying pictures reported may reflect the rapidity or severity of the original vasospastic lesion.

Corroboration for a vasospastic element in the lesions of the pulmonary vessels is to be found in the occasional lowering of pulmonary vascular resistance by means of drugs. The subject of the effect of drugs on the pulmonary circulation has been well reviewed by Halmagyi.[10] Among the drugs that have been used are acetylcholine,[4,41] Priscoline,[17] and reserpine;[43] all showed greater or smaller degrees of success, but were usually transient in their action. Halmagyi[39] has been successful in preventing death from experimentally produced pulmonary embolism by the use of isopropylnoradrenalin. The employment of this drug in a series of patients with a septal defect and the Eisenmenger reaction produced some fall in pressure, but only of a transient nature.[44] The drug has not been tested in idiopathic pulmonary hypertension. The use of antiserotonin substances as a means of reducing functional pulmonary vascular resistance was suggested by Halmagyi[39] and James in view of the powerful pulmonary vasoconstricting action of serotonin found by Blank[44] in newborn rats. A serotonin antagonist (1,methyl-d-lysergic acid butanolamide tartrate—UML 491, Sandoz) was without effect in one patient with idiopathic pulmonary hypertension and in one patient with the Eisenmenger reaction.

Genetic influence in the determination of the onset of the disease cannot be ignored since the disease has been reported in the same family.[47,8] Antigens perhaps may produce their adverse reaction more frequently in those with a genetic inclination.

Summary

The evidence which has accumulated about idiopathic pulmonary hypertension would suggest that it is an acquired disease.

In certain instances a relationship is suggested between idiopathic pulmonary hypertension and diseases of an immune nature and between idiopathic pulmonary hypertension and febrile illness.

The findings in the lungs at autopsy could be the result of high pressure caused initially by vasoconstriction.

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The use of artificial cardiac pacemakers

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Pacemaker therapy is used in the case of Stokes-Adams seizures due to a standstill mechanism for patients who are refractory to an adequate trial of drug therapy for all patients whose seizures are due to intermittent ventricular fibrillation and for those patients with or without seizures in whom a slow ventricular rate cannot maintain an adequate cardiac output and in whom congestive failure or chronic cerebral manifestations are severe Several types are now available including external pacemakers intracardiac catheter pacemakers, total implants partial implants and the more recent atrioventricular pacemaker

External pacemaker An external pacemaker designed to stimulate the ventricles through the closed chest wall still has an important place in the management of cardiac standstill In conjunction with an oscilloscopic monitor which triggers the pacemaker after a designated period of standstill (usually 6 seconds) it can be used as a precautionary device in a patient in whom the clinical situation suggests a high likelihood of Stokes-Adams seizures or in a patient with intermittent seizures while a trial of drug therapy is in progress.

Small battery-operated external pacemakers although without oscilloscopic monitors are also available These are of great value when transporting the patient with Stokes-Adams seizures from home to hospital from hospital to hospital or even within the hospital to the x ray department or operating room so that cardiac stimulation can be instituted if needed

For all these devices the voltages should initially be tried at 70 to 80 volts, with increases to 150 volts as required A heart rate of 60 beats per minute is adequate

The disadvantage of these devices is that they can be used for actual pacing for only short periods of time Pain and electrical burns of the skin are limiting factors. The patient must be heavily sedated and a narcotic analgesic administered for pain

Intracardiac catheter pacemaker Whenever a physician trained in the techniques of cardiac catheterization is available the intracardiac catheter method is the initial method of choice for continuous pacing

In this technique, a woven nylon catheter which contains two insulated wires (the bipolar type) is passed via the external jugular vein into the pulmonary artery and then withdrawn into the outflow tract of the right ventricle. This must be done entirely with fluoroscopic control since the system is not designed for monitoring blood pressure Direct endocardial contact is desirable but not absolutely necessary The terminals are attached to a battery type of pacemaker The pacemaker rate is set at 60 per minute when standstill is the mechanism at 75 per minute or even 80 per minute in ventricular fibrillation types, and then the machine is turned on The current is adjusted to 1 or 2 milliamperes above the minimum required to capture ventricular responses One then tests the

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stability of catheter position by cough, inspiration and expiration, and rolling the patient from side to side and into the sitting position, with direct observation for persistence of pacing on a monitor oscilloscope. Once optimal positioning is achieved the catheter is fixed in place in the neck with a No. 00 braided steel wire suture.

The complications of this method have been considerably reduced in the past few years. Premature contractions are not uncommon in the first few days after installation of the intracardiac electrode; on rare occasions either quinidine or procaine amide is employed to diminish ventricular irritability. Anticoagulants formerly were used routinely but are now selectively omitted with little or no clinically observed deleterious effects. Intramural breaks of the wire are rare; external breaks of the wire at the positive or negative poles are not uncommon but are readily repaired. Minor malpositioning is unimportant since direct endocardial contact is unnecessary. If the catheter advances spontaneously into the pulmonary artery, pacing sometimes can be maintained by markedly increasing the milliamperage until the catheter can be withdrawn into the ventricle. If it should fall back into the right atrium, no pacing is possible without repositioning. Late infection through the sinus is occasionally a problem, especially in the diabetic patient, and may require withdrawal of the catheter and re-insertion at another site.

Some physicians consider this the method of choice for long term pacing; others prefer implanted pacemakers. Catheter pacing is certainly the best method when there is reason to suspect that the Stokes-Adams mechanism is a temporary phenomenon. It is probably a necessary preliminary to an implanted pacemaker and is disconnected in the operating room just as the implanted pacemaker is activated. In this way the patient's heart rate is maintained at a satisfactory level during induction and thoracotomy when the chest is being opened, at which time an external pacemaker is impractical.

It is also useful for setting at various levels the heart rate of a patient with markedly low cardiac output so that his output can be measured at these various levels and a proper long term rate chosen.

Total implants. The total implantation of pacemakers is being used far more frequently than are the other methods. In this technique positive and negative electrodes are attached to epicardial ventricular muscle with braided steel or coiled platinum spring leads. These are connected via a subcutaneous tunnel to a battery pacemaker buried in the abdominal wall. A key problem of this device is the duration of battery life which extends up to 5 years.

Experience with this method is generally quite satisfactory. The major problem in long term use is breakage of wires and coils, a problem it shares with the other methods. It requires anesthesia and thoracotomy. Moreover, rate and milliamperage output in many models are not easily adjusted, often requiring another surgical procedure. The inability to control rate is a limiting factor in the activity of the patient. Long term use may occasionally result in the need for greater milliamperage either because of fibrosis around the electrode or because of minor loss of contact.

Several methods involve a totally implanted set of pacemaker electrodes, activated through the unbroken skin by an external rate and/or source of power. In one type, this is an induction coil which can be used optionally to modify the rate of an otherwise totally implanted fixed-rate pacemaker. In others external radio-frequency coils or induction coils supply both the rate and the energy to internal receivers. These methods have not yet eliminated wire breakage and have added greater complexity to achieve greater control. It is regrettable that the long term results and complications of these pacemakers have been reported in only a small percentage of the patients in whom they have been used.

Atrioventricular pacing. Another recently introduced method has a totally implanted battery pacemaker which fires in response to an atrial myocardial pickup rather than at a fixed rate. This apparatus contains a filter to block atrial tachycardia and converts to fixed ventricular pacing in atrial fibrillation. This would appear to be the most physiologic system available, but experience with it is limited and the problem of wire break-

Electrosleep as a method of neurotropic therapy of patients with hypertensive disease

One of the possible forms of therapy of hypertension is treatment with sleep this is based on Pa lov teaching on the medical role of protective inhibition in the therapy of some diseases.

Clinical experience has show that all types of therapy with drugs may be associated with toxic effects. Therapy by the induction of sleep is promising because of its freedom from toxic effects. Electrosleep is method of inducing sleep whereby the central nervous system is stimulated with an impulse current of small mplitude and low frequency by electrodes positioned on the mastoid processes Patients in the first and second stages of hyper tensive disease ha received therapy with electrosleep t the Academy of Medical Sciences, U.S.S.R since 1953

Method I the electrosleep procedures, constant and nchanged contact between the electrodes and ie surface of the skin is of great importance Dou- d electrodes which had tw points of contact were used. Electrodes connected t the negative terminal of the source of current were placed on the closed eyelids of both eyes, nd electrodes connected t the positive terminal of the source were placed on both processu mastoideus.

Only when the patient is i *completely free* and comfortable position bed with the electrodes properly pplied is it possible t achieve sound sleep rapidly

The procedures of electrosleep were conducted daily after breakfast (from 11 A.M until 1 P.M) and continued for 30 minutes to 2 hours. The first two *or three procedures were conducted without current,* in order t accustom the patient t the feeling of the pplied electrodes. Seventeen t twenty procedures were employed in the course of treatment. For the treatment of patients with hypertensiv disease the impulse current which was used had the following characteristics constant polarity rectangular shape, 0.2 msec duration, peak amplitude of 15 t 18 ma., repetition rat p t 80 per second average current of 20 to 25 μa. At the beginning of the procedure the ampl tude of the current was increased gradually t it final value in 3 minutes, nd t the end of the procedure it reduced gradually also in 3 minutes With the mplitude of the current just below that which caused npleas t sensation faster nd deeper sleep was obtained. A result of the patient adaptation t the current it was necessary to increase the mplitude of the current with each proced re but not p t level which caused pleasant sensations.

At the end of the procedure after the current was switched off and the electrodes were put way the patients were forbidden to open their eyes t once d to look t bright lights til the eyes were adapted.

I the treatment with electrosleep a fou -channel pparatus using Professor Liventsev ystem of electron-tube pulse generation was employed The repetition rate of the impulses ca be varied from 5 t 120 per second. A cathode-ray oscilloscope is sed t measure the mplitude of the current passing through the electrodes t each patient

Treatment with electrosleep is begu on the seventh or eighth day of hospitalization, by which time the patient has become accustomed to his en ironment nd his blood pressure has stabilized. I the course of treatment with electrosleep consistent changes i the patterns of sleep of the pa tient were observed. After five to seven treatments, the duration of noct rnal sleep wa longer nd the patients felt better in the morning After ten t twel e treatments, sleep occurred fter dinner pro*viding rest during the day Finally sleep occurred during the procedure itself* E entually in the course of therapy the erage t tal duration of sleep was 8 to 12 hours per day The nocturnal sleep wa easy and dreamless, nd the patient felt refreshed i the morning I terestingly the patients felt desire for sleep on Sundays from 11:00 A.M. to 1:00 P.M the time when they received their treatment d ring the week.

A systematic decrease of 10 t 15 mm. Hg i ystolic pressure nd of 5 to 10 mm. Hg i diastolic pressure wa noted t the end of each treatment I the initial fi t eight treatments this decrease as transitory in some patients, nd the blood pressure returned t pretreatment levels after 1 t 2 hours. However by the end of the course the blood pressure was usually fixed t level lower by 20 to 30 mm. Hg systolic nd 10 t 20 mm. Hg diastolic The changes in blood pressure did not correlat closely with the duration nd prof ndity of sleep. Incidentally decrease in the i tensity of precordial pains un related t coronary therosclerosis nd decre e in the frequency of extra ystoles were noted

It ha been show experimentally that the elec trical impulse is conducted int the central nervou system from the sites of the stimulating electrodes,

so that actual stimulation of the brain is possible. However it was thought to be advisable to investigate the factor of psychic suggestion in the effect of electrosleep therapy. For this purpose we studied a group of 35 patients in the first and second stages of hypertensive disease who were complaining mainly of disturbances in sleep, including complete insomnia.

The same procedure was followed with this group as with the other except that the first six to eight treatments were conducted without current ("zero idle procedures"). The electrode masks were connected in the same fashion as in those patients who were actually stimulated and the patients believed that they were being stimulated. In the majority of patients (27) no significant changes were observed during the sham treatments. Nocturnal sleep was not restful and dreamless, sleep did not occur during the treatment, the blood pressure did not change and the state of health remained unsatisfactory. Eight of the patients experienced somnolence during the procedures, but their state of health did not improve and the blood pressure was not lowered. They continued to complain of fatigue, weakness, and headache.

Later the sham treatments were replaced by actual stimulation in these same patients. In the majority of patients a marked decrease in arterial pressure occurred immediately after the current was switched on. In some a state of sleepiness developed during the first actual treatments. In those whose sleep was not improved, an improvement in the general state of health occurred immediately after the treatments. Electrosleep eliminated insomnia in patients with hypertensive disease of the second stage whose disturbances of sleep had been refractory to therapy with pharmacologic agents.

An impulse current of the parameters used evidently exerts an influence on the disturbed neurodynamic processes in patients with hypertensive disease diminishing the force of excitatory processes and augmenting the weakened inhibitory processes. Augmentation of the inhibitory processes produces in some cases a decrease in blood pressure. Because electrosleep does not always produce a decrease in blood pressure, we have used recently a combined regimen of electrosleep plus ganglion blockers and spasmolytic agents.

The selection of patients for electrosleep therapy is important, since there are objections to the use of electrosleep in patients whose prevailing excitatory processes are pronounced.

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White muscle diseases

Extreme pallor of involved skeletal and cardiac muscle is characteristic of a fascinating and ill-defined group of degenerative disorders of lower animals. Similarities are such that the following general description applies to the different syndromes which comprise the group[1]. The lesions are scattered, show predilection for weight-bearing muscles and usually involve portions of a muscle rather than the entire muscle. Symmetrical involvement of skeletal muscle is the rule. Cardiac involvement is most prominent in the free wall of the left ventricle although septal and papillary musculature may show similar changes. At the microscopic level spotty involvement is noted and scattered fibers or portions of fibers of diseased tissue are interspersed in areas of what appears to be normal muscle. Of course, this is dependent upon the severity of the process so that all of the muscle fibers in an area may show the changes of white muscle disease. As a rule the inflammatory reaction is not excessive and consists of infiltration by leukocytes, macrophages, lymphocytes and histiocytes. Fibrosis and calcification are common, the latter often being quite extensive. The muscle fibers exhibit all degrees of destruction from hyalinization to coagulation necrosis. Loss of sarcoplasm with persistence of supporting structures may occur. Pyknosis or disappearance of nuclei is common as is fragmentation and disappearance of fiber structure. In other instances the muscle fiber appears to be intact although its cytoplasm is greatly reduced. Frequently myofibrillar extensions and the appearance of distorted syncytial nuclei are observed and interpreted as unsuccessful attempts at muscular regeneration. Hemorrhage and edema may occur.

The clinical picture presented by these unfortunate animals is determined by the location and degree of muscular involvement. In the more common form, impaired voluntary movement occurs, with muscular weakness, lassitude, refusal to nurse, bawling, difficulty in swallowing and a tendency to arching of the back. The latter is due to the shifting of weight, as a result of which the back feet are placed more forward and the forward feet more backward than normal. Contraction of affected muscles may occur eventually. Motor paralysis, prostration and death is the usual course although spontaneous recovery has been reported, as has subsequent relapse. Any time in the course of the disease cardiac insufficiency can develop. This complication is manifested by weakness, dyspnea and frothy or blood-tinged nasal discharge. Death occurs within a matter of hours. In the acute form of white muscle disease which is less common the picture

is one of congestive heart failure which terminates fatally within hours of its appearance. The symptomatology is as described previously. Often such instances of acute cardiac insufficiency are precipitated in an apparently healthy animal by strenuous exercise. Histologic examination may reveal extensive cardiac involvement with only limited disease of the skeletal musculature. For these reasons affected animals whose range of activity is limited may not show the disease during life.

White muscle disease, as described above, has been found in young lambs ("stiff lamb disease") and in calves. In some instances the disease appears to have been caused by a deficiency of vitamin E and to have been cured or prevented by the addition of this vitamin to the diet. However there is another form of white muscle disease involving lambs and calves. In this latter instance the pregnancy diet of the mothers was alfalfa or clover hay which had been grown in recognized areas of white muscle disease. Although alpha tocopherol is of no benefit in this variant of the syndrome, the addition of trace amounts of selenium to the diet provides almost complete protection.

There are several other disease processes which are often included in any discussion of the white muscle diseases. Gossypol, a usual constituent of cottonseed meal, can cause a white muscle syndrome in swine, provided that this type of meal constitutes a sufficiently large portion of the diet. The clinical picture is that of progressive congestive heart failure. Postmortem examination reveals cardiac dilatation and hypertrophy in association with variable degrees of myocardial degeneration. Severe centrilobular hepatic necrosis is usually noted. The skeletal musculature shows involvement of the white muscle disease type in more than half of such cases. Azoturia, or acute paralytic hemoglobinuria, occurs in horses and is characterized by muscular lesions which are very similar to those of nutritional white muscle disease. On the other hand, asymptomatic swine fed on long-stored maize have been found to have white muscle type of lesions on routine slaughter. Finally a choline-deficient diet has resulted in this type of muscular lesion in rabbits.

In summary, the white muscle diseases are of interest to the cardiologist because of the concomitant association of disease of skeletal and cardiac muscle, the frequency and severity of myocardial disease, the diverse etiological factors which must be considered, and the possible relationships to nutrition and trace metals.

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The value of percutaneous renal biopsy in the hypertensive subject

It has now been more than 10 years since Iversen and Brun published the first report of percutaneous renal biopsy in man. Since that time well over 4,000 cases have been reported[2] and nearly every known "medical" renal disease has been studied by this technique. Several new pathologic and clinical entities have been described including subacute bacterial nephritis,[illegible] focal glomerulonephritis,[illegible] and benign, recurrent hematuria with "focal nephritis."[illegible] Renal biopsy has proved to be a safe procedure, and its clinical value has gradually emerged.

It has proven useful in the following situations: (1) determination of etiology in the nephrotic syndrome and selection of patients for adrenocortical steroid therapy; (2) diagnosis of "latent" glomerulitis in disseminated lupus erythematosus and selection of appropriate patients for high-dosage steroid treatment; (3) diagnosis of renal amyloidosis; (4) selection of patients with acute anuric renal failure for hemodialysis;[illegible] (5) evaluation of prognosis in nephrocalcinosis due to hypercalcemic states; (6) kidney culture in chronic pyelonephritis.[illegible]

(7) evaluation of diabetic nephropathy [23] and (8) evaluation of diffuse undiagnosed renal disease.[24]

The value of percutaneous renal biopsy in the evaluation of the hypertensive patient has been largely unexplored. Recent observations[25] suggest that there may be a significant number of hypertensive patients with silent glomerulonephritis or occult chronic pyelonephritis. In this group, renal biopsy may be the only technique which allows accurate diagnosis. It is important, from a practical viewpoint, to recognize patients with occult pyelonephritis. Although it may be uncommon, reversal of hypertension has been occasionally reported after antibiotic therapy.[26] In 1957 Saltz, Sommers and Smithwick[25] reported the results of *open* renal biopsies, obtained from 1,251 hypertensive patients at the time of sympathectomy. Chronic pyelonephritis, which had been unsuspected clinically, was present in 13.5 per cent of these patients. Thus, it appears that a significant proportion of patients who are thought to have essential hypertension have occult pyelonephritis. Percutaneous renal biopsy is of diagnostic value in this group.

The potential usefulness of renal biopsy in the study of patients who are thought to have renovascular hypertension is also largely unexplored. When a hypertensive patient is found, by arteriography, to have a lesion which partially obstructs a renal artery, the assumption generally made is that the arterial lesion is responsible for the hypertension. Although this is the case in many of the patients, there are a substantial number in whom the occurrence is coincidental. Surgery in this group will not alleviate hypertension. Poutasse, Dustan and Page[27] recently reported their results in the surgical treatment of 80 patients with demonstrable renal arterial lesions. Only 60 per cent of this group had a cure of diastolic hypertension.

The finding, at autopsy, of narrowing of the renal arteries due to atherosclerotic plaques, in the absence of hypertension, is not uncommon. Blackman[28] noted stenosis of one or both main renal arteries in 86 per cent of 50 patients with hypertension and 10 per cent of 50 nonhypertensive patients. Similar results were obtained by Richardson.[29] Oppenheimer and associates[30] described several instances of unilateral constriction of the renal arteries in the absence of hypertension.

From the above-mentioned evidence there can be no doubt that renal arterial narrowing may exist in the absence of hypertension, and, also, that renal arterial narrowing and hypertension may coexist without any causal relationship. Indeed, from Blackman's data it would appear that hypertension may actually contribute to the development of atherosclerosis of the renal arteries, much as it does to the development of atherosclerosis in other vessels.

Therefore, if we are to spare a large number of patients from surgical morbidity, including possible nephrectomy, we need a reliable method of determining whether a given renal arterial lesion in a hypertensive patient is a significant lesion, i.e., whether it is actually giving rise to the hypertension. The use of split renal function studies by bilateral ureteral catheterization, bioassay of renal vein plasma for vasoconstrictor activity,[31] and radio-Hippuran renograms[32] have contributed a considerable amount of valuable information in the evaluation of the significance of a given lesion. Percutaneous renal biopsy may also make a contribution by the demonstration of (1) hyperplasia or hypergranularity of the juxtaglomerular cells on the side of the lesion, with a decrease on the contralateral side;[33-35] (2) "ischemic" atrophy of the proximal convoluted tubules on the side of arterial narrowing;[36] (3) a difference between the kidneys in the severity of arteriosclerosis or arteriolosclerosis (the renal vasculature on the side of a significant stenosis is protected from the effect of systemic hypertension)[37] and (4) a difference between the kidneys in the kidney pulse tracing (the tracing obtained from a kidney with a significant arterial obstruction is characterized by a decrease in amplitude and by a slower rate of rise).[38]

In addition, renal biopsy may offer other valuable information. The presence of advanced vascular disease in the contralateral kidney or occult pyelonephritis in either kidney may result in the perpetuation of hypertension after surgical correction of significant obstruction of a renal artery.[39] Knowledge that such changes are present is of great value to the physician in planning his approach to the patient.

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Uremic acidosis Some alternative views

A widely accepted explanation for the pathogenesis of cidosis in renal disease with or without uremia ttributes both varieties to diminished secretion of hydrogen ion by the bnormal nephron.[a] This theory i turn rests upon another even more thoritati hypothesis which holds that the normal kidney converts lkaline glomerular filtrate into acid urine by exchanging hydrogen for sodium. It depends ery largely upon the demonstration by Pitts and Alexander[4] that the titratable acidity of the urine far exceeds that which ca be accou ted for by the estimated rate of glomerular filtration especially when subjects are infused th buffers, such as phosphat or creatinine.

Ther ca be no doubt that carnivorous diet presents the renal tubules th more nions tha can be safely excreted as sodium salts so that other cations are called pon to handle the load. Although H seems to be the most importa t cation i vol ed one must not suppose that the only possible mecha nism consist of bidirectional movement of sodi m nd hydrogen across tubular epithelium. Brodsky

and Carrasquer[1] ha listed alternati e explanations urinary acidification could be due to tubular secretion of H_2PO for example or to resorption of $HPO^=$ or HCO Mensaker[4] nd Briggs ha both suggested that the process consists of resorption of an alkaline resorbat (N OH N HCO). Hydroxyl ions are provided by the ionization of ter since the reaction H × OH = kH$_2$O is instantaneous, the supply of OH should keep pace ith resorption of N The resorbed NaOH is buffered by H_2CO so that the inhibition of urinary acidification by carbonic-anhydrase inhibitors is accounted for as well by this theory as by the orthodox theory of H secretion. To deny that H ions are secreted, however is not to question the conventional idea that NH diffuses out of the cells of the distal segments into the tubula lumen provided that the fluid therein is strongly acid in reaction this mechanism may only serv to prevent excessiv urinary acidity.[10]

Other observations support the idea that even i disease the nephrons function uniform nd relatively normal manner Bricker group has shown that except for m nor changes attributed to osmotic diuresis through reduced number of nephrons, the excretion rates of H and NH as well as the absorption of HCO_3^- are ll normal in experimental canine nephritis if they are related t volume units of glomerular filtrate. This ork support Platt suggestion[16] that residual nephrons in chronic Bright disease perform normal fashion and increase their excretory rates under the stimulus of increased filtered loads.

Secondly the uremic patients studied by Briggs and his colleagues t the Medical College of Georgia excreted normal quantities of acid hen the diet was so arranged that the urinary output of phosphat nd sulfate equaled that of the normal controls. Indeed the pH of the urine was little lower than normal, and the titratable cidity as correspondingly greater

An pparent nomaly in this study deserves comment. The nephritic patien excreted less NH ion than did the controls hence their net proton ou put (titratable acid plus NH) as also less. At first glance, this ppears to offer an explanation for the acidosis, but calc lation of the rate of total sodium bicarbonate regeneration shows that this phase of tubular activity as nearly the same in both groups This alue is obtained by adding the potassium ou put t the lue for titratable acid plus ammonia TA nd NH representing the excess of fixed anion over fixed cation It is importa t to note that he uremic patien ho is ble to eat normal diet maintains normal plasma N oncentra ion despite the diminished ou put of TA and NH contradiction hich is removed by correcting for K output.

The rationale for this K orrection ma be based on more K exchange of K for N in the nephritic patient reclamation of N thout acidification A lternati e, the authors suggest that the urinary K is secreted, chiefl by the distal tubules as KHCO since Cl is not secreted into the tubular lumen. The increased fla of the urine after he administration of KCl[18] is understandable on this basis This $KHCO_3$ then neutralized equivalent qua t of liberated acid

Excretion of N w essentially equal in the two groups, but the nephritic patient wasted slightly greater mount of K The acid-loading in their study was thought to be responsible for this excessive excretion since acid-loading i the nephritic patient brings an excess of potass m-rich intra cell lar fluid into the plasma. Therefore without acid-loading the t o groups should ha excreted nearly equal qua tities of K as well as Na Cl$^-$ SO$^=$ nd H^+PO And with diminished secretion of KHCO and hence less neutralization of liber ted acid the sum of t tratable acid + ammonia should hav been essentially the same in the nephritic and non-nephritic groups ithout correction for K

Briggs long ago interpreted the excessive acidity of the urine i cases of uremia to be the result of larger pool of luminal fluid flowing more swiftly through hypertrophied nephrons in state of osmotic diuresis, i.e. to diminished contact of liberated acid ith ammonia-producing epithelium

Strong metabolic acids come from three principal sources the oxidation of sulphur-containing amino-acids the hydrolysis of ester-linked phosphate compounds, and the incomplete oxidation of fats and carbohydrates t such acids as aceto-acetic and lactic The pathwa by which the body disposes of the protons of these strong acids has been the subject of some controversy Elkinton[4] upholds the classic iew that "Metabolic hydrogen ion is excreted through the kidney " but the Georgia group[4] say that The kidneys are therefore little concerned th the disposal of metabolic proton. These orkers believ that strong metabolic cids must react with bicarbonate of tissue fluids, releasing H_2CO which is then disposed of by the carbonic-anhydrase mechanism in the lungs. The urinary protons re produced de novo in the distal tubule by the mechanism hich is concerned with the reclamation of Na from salt of waste anion. Elkinton advocated the use of formula which he took to be coefficient of plasma clearance of hydrogen ions

UV va + 1/plasma CO_2,

but this could be written as

UV × plasma CO_2.

I the patients of the Georgia study and in the controls also, ll of whom received the same diet and the same acid-load, the output of titratable acid plus ammonia was nearly identical when corrected for K The factor UVa of Elkinton equation could, therefore, on comparable diets be replaced by constant Low alues for the coefficient in patients with renal impairment are consequently due t low plasma CO_2, nd this, in turn, is due chiefly to retention of sulfat and phosphate.

Ester-lined phosphates are hydrolized during the process of digestion, nd phosphoric acid, hich is split off is instantly neutralized by $NaHCO$ of the digestiv fluids—the pH of the digest ranges from about 5 in the duodenum to 6 I the ileum. I this pH range 90 per cent or more of the phosphate is bsorbed as N H_2PO but rinary phosphate, in the icinity of pH 6, is predominantly monobasic. It seems proper therefore, to regard the phosphate ion hich is retained in uremia as H_2PO^-

Thus, uremic acidosis may still be due to replace

ment of plasma HCO by anions (SO + H₂PO) which re weak proton ceptors—the result is elevation of the oncentration of plasma hydrogen ion Because our studies contain some unique features w hope that they will be repeated and extended by others. The result did not support th iew that uremic acidosis is d t tubular dysfunction Acidific tion of the rine may be due t the resorption of lkali rather than to the secretion of id but t present e see no w y t decide which of these lternatives view is orrect

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Book reviews

Electrovectorcardiografia Clinica. By Pedro Cossio and Victorio Fecorini, M.D. Facultad de Medicina de Buenos Aires, Argentina. Buenos Aires, 1962, Fundacion Cossio, 402 pages.

This is a good book on clinical electrovectorcardiography. The presentation is sound, simple and clear and the illustrations are very good. As the title indicates, the discussions are concerned primarily with the vectoral approach to the analysis and interpretation of the electrocardiogram. The authors have successfully achieved their purpose of presenting rather difficult ideas to beginners in the field. This book should prove to be of value to students, general practitioners and cardiologists.

Blood Volume. By Solomon N. Albert, B.A., M.D., Diplomate, The American Board of Anesthesiology, Senior Attending Anesthesiologist, and Director of Research, Department of Anesthesiology, Washington Hospital Center, Washington, D.C. Springfield, Ill., 1962, Charles C Thomas, Publisher, 175 pages. Price $8.50.

This monograph on blood volume suffers from a number of deficiencies. Too much space seems to have been devoted to an attempt at simplified discussion of hemodynamics using diagrams which serve to confuse rather than clarify. On the other hand, the central problem, the clinical use of blood volume measurements, the establishment of meaningful normal values for a population with wide variations in body habitus, is dealt with in only a very cursory manner. There is also the annoying habit of using references to review articles rather than the primary sources when citing evidence.

The second half of the monograph, which is devoted to technology, furnishes a good account of some of the methods employed in determining blood volume.

Probleme der Zentralnervösen Regulation. Bad Oeynhausener Gespräche V. Edited by L. Delius, H. P. Koepchen, and E. Witzleb. Berlin, 1962, Springer Verlag, 102 pages, 32 illustrations. Price DM 38.

That this volume is published as *Gespräche* implies that the authors consider it as an informal presentation, but this does not detract from it. The volume contains much interesting thought and information on basic biologic and physiologic rhythms and regulations. Of the nine articles, five are concerned with circulatory functions. The consideration of the history of exploration of cardiovascular regulations and rhythms, which goes far back into the nineteenth century. Emphasis is placed on the theoretical interpretation of circulatory autoregulation, but even more important is the attempt to analyze rhythm and regulation of circulatory functions in the wider perspective of various biologic rhythms from short-term to long-term periods (fractions of seconds to yearly rhythms). From this point of view, Goldenhofen analyzes peripheral circulation. G. Hildebrandt discusses regulations of pulse rate, blood pressure, respiration and regional circulations. H. P. Koepchen reports on fluctuations in blood pressure in correlation with respiration and the effect of autonomic reflexes, and K. Meckelke investigates the regulation of blood pressure in disturbances of the autonomic nervous regulations. It is intriguing that the phase relationship between various circulatory functions and between blood pressure and respiratory cycles may be useful for the separation of healthy people from patients with circulatory disturbances. The book is a stimulus for further research.

Although the volume contains much interesting recent, condensed experimental information, its main value lies in the attempt to explore general biologic principles involved in the various biologic regulations. Therefore, this volume is rewarding for all who are involved in clinical physiologic and, particularly, cardiovascular research, since as mentioned the larger part of the book is devoted to cardiovascular functions.

The Theory and Practice of Anticoagulant Treatment. By L. Poller, M.D., Consultant Pathologist, South Manchester Group, and Hematologist, Withington Hospital, Manchester, England. Bristol, 1962, John Wright & Sons Ltd. Baltimore, 1962, Williams & Wilkins Company, 150 pages. Price $6.50.

This small volume presents an excellent summary of the theory and practice of anticoagulant therapy. After a brief introduction which is concerned with the clinical incidence of thrombotic disease and the normal blood clotting mechanism, the prevailing theories of the pathogenesis of thrombosis are summarized. The next two chapters deal with the practical aspects of the use of heparin and the Coumadin-indandione drugs. The important aspects of proper laboratory control are succinctly described. The evidence for and against anticoagulant therapy in various clinical situations is then presented in summary form. An outline of useful technical methods is included and followed by a very good index.

The review of the literature has been well chosen and is presented in a critical manner which has obvious advantages over a simple summary. This style of writing is lucid and is easy to read and understand. The graphs, illustrations and charts are well chosen.

It is refreshing to read so critical a summary of the recent literature on such a complex and controversial problem. This is quite valuable and suggests both personal experience and

maturity on the part of the thor which notably enhances the value of the book. I lew of the rapid progress which is being made n the field of blood coagulation and thromboembolism it is obvious that certain aspects of a work such as this may soon need revision. However this does not detract from this excellent critical survey which will prov to be of value to all those interested in thromboembolic disease and anti coagula t therapy

Announcements

THE LIFE INSURANCE MEDICAL RESEARCH FUND is now recei ing APPLICATIONS FOR AWARDS to be ilable July 1 1964 as follow *U 11 November 1 1963* for gra ts t institutions in aid of research on cardiovascular problems Support is ailable for physiological biochemical, and other basic work broadl related to cardiovascular problems, as well as for clinical research in this field

Further information and pplication forms may be obtained from the Scientific Director Lif Insura ce Medical Research F nd 1030 East Lancaster A Rosemont, Pa

THE THIRTEENTH ANNUAL CONVENTION OF THE AMERICAN COLLEGE OF CARDIOLOGY will be held t the Roosevelt Hotel, New Orleans, Louisiana on Feb *12 16* 1964

Abstracts of papers intended for the scientific program should be sent before Oct. 1 1963 to Dr George E. Burch 1430 T lane A e., New Orleans 12 La. Abstracts should be pproximately 250 words in length The original nd three copies are required. Special niform copy sheets will be supplied on request

Scientific and commercial exhibitors should write t Dr Philip Reichert, Executi Director Americ College of Cardiology Empire State Bldg New York 1 N Y

THE VII INTERAMERICAN CONGRESS OF CARDIOLOGY will be held in Montreal, Canada, from J ne 14 to 19 1964 nder the joint auspices of the Canadian Cardiovascular Society and the Interamerica Society of Cardiology (Sociedad Interamericana de Cardiología).

A broad scientific nd social program is being planned and it is expected that there will be about one thousand cardiologists in ttendance from the United States, Latin America nd Canada. The Chairman of the Organization Committee is Dr Pa l David. The Chairma of the Scientific Program Committee is Dr Jacques Genest.

Enquiries in regard to the Congress should be directed to Dr Jonathan Ballon Secretary VII I teramerican Congress of Cardiology 2052 St. Catherine St., West Suit 114 Montreal 25 Quebec, Canada.

THE YOUNG INVESTIGATORS AWARD of the American College of Cardiology—February 1964

All interested workers are invited to writ E. Grey Dimond M D Chairma Young Investigators Award Committee, Box 1533 La Jolla Calif

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Editorial

A-V dissociation
A proposal for a comprehensive classification and consistent terminology

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After several recent articles on the subject of A-V dissociation,[1-4] the last one only a few months ago in this JOURNAL, another one would seem redundant were it not that the lack of a uniform terminology and the disagreement among different authors concerning some basic concepts have prevented the assignment of this common disorder to its proper place in a systematic presentation of the broad spectrum of cardiac arrhythmias. Yet such a system is indispensable not only in teaching the interpretation of simple and complex arrhythmias to students and postgraduates, but also in providing the practicing cardiologist with the possibility of evaluating any of the clinical varieties of A-V dissociation in proper perspective.

What then are the principal points of disagreement and what are the problems facing an attempt at a unified semantic presentation? Disagreement exists not only in the interpretation of the term *interference* as introduced in this context by Mobitz, but also in regard to the question whether the term *A-V dissociation* should or should not be used in the presence of A-V block regardless of the rate and origin of the ectopic cardiac rhythm. Is interference a manifestation of the normal refractory phase of myocardial tissue which results from the collision of two impulses coming from opposite directions or the same direction, or does it imply a disturbance of the rhythmic action of one pacemaker by the action of another? (Proponents of the latter concept[?] do not hesitate to use the former view in another context, for instance, by recognizing parasystole with simple interference.) And does not the concept of A-V dissociation per se, accepted by all authors, imply some impairment of the transmission of impulses through the atrioventricular junction, at least in a retrograde direction, to keep atrial and ventricular action separate and independent? And finally, is it at all possible to find a unifying viewpoint that will cover the numerous facets encountered in clinical electrocardiography in connection with this particular and controversial type of disorder of the heartbeat?

It would appear that a pitfall common to all previous attempts to bring some order

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CAUSES (1) Slowing ... (2) Acceleration ... (3) Block (4) Combinations

EFFECT A V DISSOCIATION

VARIETIES COMPLETE INCOMPLETE With

Fig. 1

int this confusion is the lack of recognition that A V dissociation is *never a primary disturbance* of rhythm to be presented as such in textbooks and headings of special communications but rather the *consequence* of some other more basic disorder. To draw an analogy it can be compared with another (a trivial) disorder of rhythm the compensatory pause after a premature ectopic beat here the secondary character of the disruption of the regularity of rhythm is undisputed and no one wishes to nor does complicate matters (a) by distinguishing compensatory pauses after single or repetitive premature beats from those after a run of paroxysmal tachycardia (b) by separating truly compensatory pauses after premature beats of ventricular origin from those caused by early junctional or atrial impulses or (c) by excluding from this term instances of slow rhythm in which the occurrence of such a compensatory pause has to be attributed to an associated abnormal conduction block. Certainly a similar logic should apply to a proper classification of A V dissociation.

By putting *cause effect* and *varieties* in the foreground of a systematic classification a diagram can be devised such as is shown (Fig. 1) which coordinates all the controversial aspects and terms related to A V dissociation on the basis of well established and simple principles of cardiac physiology.

In such a scheme in which A V dissociation is employed in its strictest meaning that is independent action of atria and ventricles it is pertinent to recognize three different causes each of which can bring about the disruption of the normal link between the atria and the ventricles (1) slowing of the generation of impulses in the primary pacemaker of the heart (2) acceleration paroxysmal or nonparoxysmal of a potential A V junctional or ventricular pacemaker and (3) permanent or intermittent failure of several successive primary pacemaker impulses discharging at a normal rate to reach or to cross the narrow atrioventricular bridge. There is, however no valid reason to exclude from this basic causal classification combinations of two or three such factors, as is actually quite often the case. Some examples may be mentioned (caused particularly by digitalis) an S-A block may combine with acceleration of A V nodal impulse formation or an enhanced nodal impulse rate may develop together with depression of junctional tissue blocking all retrograde pathways to the atria or in the presence

of atrial fibrillation (or flutter). Under all these circumstances the result will be A-V dissociation. On the other hand, there is no need to imply a complete A-V block in all instances in which synchronization of sinus and ectopic rates, be they slow or rapid, maintains the dissociation by virtue of the constant collision of the two activation fronts in the A-V junction. Many a dilemma in classification can be avoided in a report by stating explicitly not only that A-V dissociation exists, but by giving the single cause or combination of causes responsible for it.

Into this framework of cause and effect one can readily fit the entire spectrum of common and rare facets consequent to and associated with the disturbed order of atrial and ventricular activation. Furthermore, one of the principal stumbling blocks in arriving at a meeting of minds concerning the controversial interpretation of Mobitz's term *interference* can be avoided by conceding that the action of dissimilar mechanisms can lead to identical results. The actual variables are: rate of discharge of *effective* impulses, their temporal relationship, and the state of responsiveness of the conducting tissues. For instance, *complete* A-V dissociation maintained by temporary synchronization of primary and subsidiary impulse formation, be it due to slowing of the former or acceleration of the latter, will change promptly to an *incomplete*[4] one with ventricular captures as soon as either pacemaker becomes unstable—without any alteration in the basic conditions that govern the facility of the A-V junction to transmit impulses. And by the same token, the passage of impulses from the atria to the ventricles, or vice versa, may be limited to single captures or may become repetitive so that the A-V dissociation yields to a period in which the entire heart is under the control of a single center—sinus rhythm or nodal rhythm with retrograde activation of the atria. Any experienced electrocardiographer is familiar with some clinical records which reveal side by side and in alternation such periods of synchronous and sequential activation of atria and ventricles—in short, an *intermittent* A-V dissociation. This is particularly prone to occur when the acceleration of formation of ectopic impulses is not associated with depressed A-V conduction, e.g., in acute rheumatic carditis or in ventricular paroxysmal tachycardia. On the other hand, given two records of the same case with comparable pacemaker rates on different dates, one having captures or retrograde conduction and the other complete A-V dissociation, one must postulate that an additional factor has come into operation, namely, a prolongation of the refractory phase of A-V junctional tissue; in short, an A-V block of undetermined degree is now associated with the abnormal formation of ectopic impulses and thereby sustains independence of atria and ventricles. Such a sequence usually occurs during digitalis medication, but it may also occur under other pathologic conditions with a tendency to involve both A-V nodal functions, especially recent posterior wall infarction and acute rheumatic fever.[18]

When conductivity of the A-V junction is preserved, be it normal or somewhat depressed, appropriately timed impulses may be able to cross it in one or both directions to cause occasional or frequent ventricular and/or atrial captures. Although a handicap to retrograde spread appears to be a feature of a physiologic or slightly prolonged state of A-V refractoriness, unidirectional antegrade block is seen only in advanced stages of A-V block, sometimes in association with a supernormal phase of A-V conduction.[33]

As a rule, ventricular as well as atrial captures in incomplete A-V dissociation are readily identified, frequently at a glance, by their premature incidence and/or their aberrant configuration. There are, however, exceptions to this rule. Thus, the capturing impulse may share ventricular or atrial depolarization with an impulse released simultaneously by the other pacemaker. Then, instead of a total capture, there will be only a *partial capture*,[7] an event expressed in the electrocardiogram as ventricular or atrial fusion beats. Or the impulse which arrives at an incompletely responsive A-V junction will be slowed in its path so that it reaches its destination with some delay or is stopped altogether. In the former case the subsequent intrinsic pacemaker cycle may appear to be foreshortened, whereas in the latter case it will be unduly prolonged—one

of the manifestations of concealed A V conduction [13]

As is evident from this brief outline all known phenomena inherent in the varied nature of independent atrioventricular beating and all associated features repeatedly documented in actual clinical records[13] can be fitted into a simple scheme in conformity with the rules of analysis of any type of cardiac arrhythmia timing of the generation of impulses in relation to normal or abnormal states of refractoriness. Although it must be recognized that the various primary disorders may differ widely in their *clinical* significance there is no need and indeed no rationale to artificially separate the various modes of their presentation which in the last analysis share a common explanation for their secondary appearance as A V dissociation

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Clinical communications

Clinical experience with the monoamine oxidase inhibitor, DL-serine-N² isopropylhydrazide (RO 4-1038), in the treatment of hypertension

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In a previous preliminary report it was shown that the monoamine oxidase (MAO) inhibitor DL-serine-N isopropyl hydrazide monohydrochloride (RO 4-1038) is a useful adjunct in the treatment of hypertension. On the basis of published data RO 4-1038 appeared to be a more potent antihypertensive agent than the MAO inhibitors iproniazid (Marsilid) and pheniprazine (Catron) and was relatively free of undesirable side effects. It is the purpose of this report to extend these observations to include a large number of patients treated for prolonged periods of time RO 4-1038 would appear to be an appropriate drug to study since (1) it is an analogue of iproniazid and thus has the typical configuration of most of the MAO inhibitors, and (2) hemodynamic studies suggest that the hypotensive effect of MAO inhibitors is attributable almost solely to their ability to decrease total peripheral resistance a desirable and unique mechanism among the clinically useful hypotensive drugs.

Methods and materials

The subjects were recruited from a "Study Group" which has been followed for at least 1 year in the Renal Hypertension Clinic at the U.C.L.A. Medical Center. These patients generally have moderate hypertension (Table I) which is considered to be stable or only slowly progressive. The characteristics of their blood pressure as well as their usual symptoms are well known since they have received various placebos and other hypotensive agents during the course of other investigations. In an effort to minimize the fluctuations in blood pressure incident to individual reactions to various physicians and surroundings the following routine is used. Patients are seen weekly or biweekly. They are instructed to lie quietly in a semi darkened room for at least 15 minutes.

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Table I. Individual data and response to therapy

Patient	Etiology	Age Sex	LVH	Fund.† (grade)	Serum creatinine (mg. %)	Control blood pressure (mm. Hg)		Dose (mg.)	Response after	
									RO 4-1038 alone	
						Supine	Standing		Supine	Standing
J. G.	E	67 M	−	1	1 0	188/108	192/110	20	170/108	162/110
N. C.	E	67 F	−	0	1 22	153/90	148/100	5 4 X wk.	140/85	125/82
I. C.	E	55 F	+	1	1 3	226/106	226/116	10	190/100	134/99
W. S.	E	55 M		[illegible]	1 5	184/102	173/110	5	166/91	141/94
L. B.	R	61 F	+	1	1 0	142/100	166/112	15	168/107	145/97
A. H.	E	63 F	+	1	1 17	181/93	187/107	20	199/98	170/88
J. P.	E	49 M	+	1	1 12	183/106	167/108	5	137/87	121/84
R. T.	E	64 M	+	2	0 77	200/110	175/113	25	173/102	154/104
G. S.	R	68 M	+	1	3 1	200/120	236/140	5	141/84	138/88
C. S.	R	44 F	+	2	0 8	186/111	—	25	184/122	168/116
I. N.	E	65 F	+	2	1 1	173/112	178/116	5	152/100	138/100
J. B.	E	49 M	+	1	1 0	200/106	168/106	10	—	—
J. W.	E	51 M	+	1	1 0	234/116	—	10	202/100	164/92
E. N.	E	53 F	+	3	0 7	174/96	182/115	15	164/100	133/95
B. N.	E	69 F	+	1	1 3	208/110	202/114	7 5	165/84	154/86
G. E.	E	66 F	+	2	0 7	180/120	172/122	5	168/98	122/95
R. W.	E	75 F	+	2	0 8	178/104	188/108	5	157/90	172/110
J. C.	E	55 F	+	1	1 3	165/85	159/109	5	158/92	126/89
L. G.	E	59 F	+	2	0 9	218/102	214/104	10	188/88	138/75
J. C.	E	53 F	+	1	1 6	202/110	191/115	10	—	—
R. E.	E	58 F	+	2	1 6	218/112	218/127	5	—	—
A. P.	E	72 F	+	1	1 1	202/109	201/120	10	184/100	125/86
J. H.	R	51 F	+	2	2 6 to 4 1	192/111	173/115	5	202/100	158/99
A. W.	E	42 F	+	2	0 9	190/116	172/118	10	150/101	128/103
L. T.	E	40 F	+	1	0 7	221/126	198/129	10	218/118	196/112
R. H.	F	41 M	+	0	1 05	190/130	180/130	25	—	—
J. H.	E	31 M	+	2	1 4	190/130	200/140	20	110/180	80/60
B. L.	R	34 M	−	2	3 4	180/120	190/126	20	—	—

E: Essential hypertension. R: Renal hypertension.
*LVH: Left ventricular enlargement by x-ray film or electrocardiogram.
†Keith-Wagener-Barker classification.
‡See text for explanation of optimal dose of RO 4-1038. Where dosage was changed after addition of chlorothiazide the new dose is
§The dose of chlorothiazide was 500 mg. twice daily.
Table I is continued on pages 154-1

4-6 wk. on optimal dose*				Response after maximum duration of treatment					
RO 4-1038 + Chlorothiazide		Chlorothiazide alone†		Duration	RO 4-1038 alone		Duration	RO 4-1038 + Chlorothiazide	
Supine	Standing	Supine	Standing		Supine	Standing		Supine	Standing
176/89 (RO4 – 7.5 mg.)	175/102	—	—	4 mo.	182/99	156/101	10 mo.	177/101	154/95
—	—	—	—	14½ mo.	173/90	190/98		—	—
140/81	123/88	168/96	146/93	5 mo	196/100	174/100	15 mo.	186/96	156/102
—	—	—	—	4 mo.	166/91	141/94		—	—
—	—	124/82	122/80	4½ mo.	168/107	145/97		—	—
175/99 (RO4 – 10 mg.)	144/92	175/92	146/88	2 mo.	190/102	162/100	2½ mo.	189/92	167/94
—	—	—	—	17½ mo.	152/97	135/99		—	—
162/108	156/104	—	—	5 mo.	183/111	147/105	8 mo.	174/111	150/106
—	—	—	—	4 mo.	193/104	198/112		—	—
200/116 (RO4 – 10 mg.)	178/92	199/120	204/118	6 wk.	—	—	7 mo.	184/117	181/108
147/101	141/101	157/111	149/105	8 mo.	155/102	156/100	3 mo.	168/114	154/110
160/98	150/98	—	—		—	—	13 mo.	150/98	150/98
236/96	174/85	206/95	174/98	11 mo.	208/88	172/82	10 mo.	166/90	166/90
160/92 (RO4 – 10 mg.)	153/96	169/98	168/108	4½ mo.	170/92	148/96	21 mo	149/84	125/84
—	—	—	—	8 mo.	208/108	200/108		—	—
140/92	142/102	172/110	168/118	6 mo.	170/120	130/106	22 mo.	160/104	143/103
167/86	162/94	159/98	174/112	4 mo.	136/70	94/62	8 mo.	162/90	138/90
168/104	127/96	178/109	165/120	8 mo.	169/101	149/102	15 mo.	180/104	136/90
176/97	156/92	177/94	190/100	21 mo.	184/98	180/88	22 mo.	176/97	156/92
162/114	122/103	—	—	11 mo.	148/131	—	12 mo.	160/111	144/88
174/103	149/104	—	—		—	—	9½ mo.	154/92	153/100
170/96 (RO4 – 5 mg.)	163/98	157 '91	156/97	7 mo.	178/96	142/84	11 mo.	168/94	153/101
161/88	141/91	218/110	187/111	3 mo	148/83	108/80	13 mo.	178/100	163/94
170/120 (RO4 – 5 mg.)	124/107	161/112	161/122	2 mo.	188/126	131/100	9 mo	177/120	136/111
221/112	184 112	—	—	3 mo.	200/114	186/120		—	—
170/110	140/100	230/140	210/140		—	—	4 mo.	164/110	160/110
150/110	130/100	180 130	190/140		—	—	10 mo.	160/100	104/122
138/100	130/96	190/120	196/132		—	—	8½ mo.	178/110	144/104

indicated in parentheses

Table I Individual data and response to therapy—Cont d

Patient	*Etiology*	*Age Sex*	*LVH*	*Fundi (grade)*	*Serum creatinine (mg %)*	*Control blood pressure (mm Hg)*		*Response after*		
								Dose (mg)	*RO 4-1038 alone*	
						Supine	*Standing*		*Supine*	*Standing*
E U	R	54 M	+	2	1 7	235/145	—	10	200/130	180/120
R. B	E	34 M	+	3	1 5	210/130	220/130	20	200/140	130/100
F B	E	34 M	+	1	1 1	172/100	178/104	20	136/81	120/82
A L.	E	42 M	−	2	12 5	180/120	—	15	150/110	120/90
H M	E	61 M	+	2	2 45	190/120	—	15	—	—
A H	E	37 F	−	1	0 8	200/110	—	5	—	—
H B	E	57 M	−	1	1 5	170/108	180/114	5	188/106	134/96
B C	E	57 M	+	2	1 4	200/112	200/120	2 5	—	—
F H.	E	56, M	+	1	1 2	200/120	—	2 5	—	—
W M	E	52, M	−	1	1 0	160/110	—	5	150/84	146/102
G. P	E	46, M	−	1 2	1 3	160/100	150/110	5	130/90	126/100
W S	[illegible]	24 M	+	2	1 2	180/100	—	30	—	—
F R.	R	51 M	−	2	3 1	190/116	174/134	20	160/100	90/70
M F	R	63 M	+	2	2 85	220/150	190/120	20	210/110	188/100
W G	R	45 M	+	3	9 6	190/110	—	20	178/100	150/90
J C	R	38, M	+	1	2 5	210/110	180/120	20	160/96	114/78
R. S	E	54 M	+	3	1 3	240/130	200/140	20	180/110	130/80
R. S.	E	59 M	+	2	1 8	226/122	208/132	20	190/100	158/100
N O	E	59 M	+	3	1 2	230/130	204/130	20	230/120	220/112
A M	E	60, M	+	3	0 7	180/90	180/120	10	150/90	100/80
E L	E	63 M	+	2	1 4	208/120	187/105	20	160/100	190/120
J H.	E	49 M	+	3	1 2	260/160	260/140	30	260/180	234/170
A. B	E	33 M	+	3	1 8	190/150	194/144	20	190/135	165/120
H B	E	36, M	+	2	1 8	204/160	—	20	188/138	164/130
I L.	R	37 M	−	0	2 4	230/130	—	20	120/70	108/70

Blood pressures are then taken by a special research nurse without comment. After blood pressures have been recorded the patients are questioned and examined by a physician The same nurse and physician participate throughout the entire study Arterial pressures are taken in the supine seated and standing positions five times successively the final recorded figures represent the averages.

Patients who had control blood pressures consistently greater than 150/100 mm Hg were randomly selected these control determinations were made over a period of several weeks immediately prior to therapy Although over 70 patients were treated with RO 4-1038 only 53 are included in the present report. Reasons for exclusion included unreliability of the patient concomitant use of antihypertensive drugs other than chlorothiazide and extreme and unexplained fluctuations in blood pressures in a few subjects.

Of the 53 patients, 41 had essential

4-6 wk. on optimal dose)				*Response after maximum duration of treatment*						
RO 4-1038 + Chlorothiazide		*Chlorothiazide alone)*		*Duration*	*RO 4-1038 alone*		*Duration*	*RO 4-1038 + Chlorothiazide*		
Supine	*Standing*	*Supine*	*Standing*		*Supine*	*Standing*		*Supine*	*Standing*	
208/120	90/70	212 126	170/120	4 mo.	224/128	148/110	1 y	190/120	170/110	
174/120	96/70	—	—		—	—		—	—	
—	—	—	—		—	—		—	—	
150 110	140 98	164 118	160, 122	5 mo.	172/122	140/96	8 mo.	180/120	150/100	
154/96	120/90	—	—		—	—	5½ mo.	166/110	160/110	
160/94	116/80	—	—		—	—	12 mo.	180/106	120/86	
120/80	96/70	139/94	134/93	5 mo.	180/110	120/70	14 mo.	130/84	110/80	
150/90	138/90	175 104	163/107		—	—	4½ mo.	150/90	130/88	
142/84	138, 80	160/90	170/96		—	—	12½ mo	130/86	140/92	
140/94	140 92	148, 100	140/107		—	—	5 mo.	160/110	124/80	
—	—	140 100	140/110	9 k	126/86	122/90		—	—	
120/82	120/90	—	—		—	—	6½ mo.	140/98	130/100	
168/120 (RO4 – 10 mg.)	150/110	270/144	240 150	6 k.	170/104	100/80	9 mo.	190/122	200/120	
144/80	130/80	200/110	170 110		—	—	12 mo.	230/130	190/120	
—	—	—	—	6 k.	170/90	170/96		—	—	
140 110	120/90	—	—		—	—	16 mo.	160, 105	180/105	
175/110	120/85	—	—		—	—	12 mo.	264/180	210, 130	
180 100	180/110	—	—		—	—	6 mo.	230/130	200/130	
105/70	104/70	168/110	150/110		—	—	4 mo.	168/98	142/100	
134/84	80/42	154 110	160, 116	16 k.	190/100	240/120	30 mo.	196/124	196/118	
130/80	150/90	—	—		—	—	12 mo.	170/110	170 110	
200, 120	196/130	—	—	4 mo.	260/180	234/140	5 mo.	228/140	232/132	
182/130	144 115	—	—		—	—	3½ mo	220/140	172/138	
156/100	100/70	—	—		—	—	9 mo.	180/120	200/150	
170/100 (RO4 – 5 mg.)	152/104	180, 110	150/100		—	—	6½ mo.	170 100	152/104	

hypertension and 12 had hypertension secondary to parenchymal renal disease (chronic glomerulonephritis, pyelonephritis, polycystic kidney disease) since the response to RO 4-1038 was similar (Table I) these two groups were combined in the evaluation of over-all results. The patients ranged in age from 24 to 75 years with an average of 52. There were 37 males and 17 females. The severity of the hypertension can be estimated by the retinal changes and evidence of left ventricular hypertrophy (radiologic or electrocardiographic) listed in Table I. Twenty two patients had mild or moderate azotemia as indicated by serum creatinine levels of 1.4 mg. per cent or greater.

A true double blind study was not attempted. The dose of RO 4-1038 was adjusted according to blood pressure response and side effects. The drug was prescribed either alone or in combination with chlorothiazide. In order to evaluate the effects of each drug separately at various times

Table II Summary of blood pressure response to therapy (see text)

	Essential					
	Supine			*Standing*		
	Number of patients	*Average BP (mm. Hg)*	*Mean BP (mm. Hg)*	*Number of patients*	*Average BP (mm. Hg)*	*Mean BP (mm. Hg)*
Control	43	198/116	143	31	189/119	142
RO 4-1038 alone at 4-6 wk.	33	174/104	127	33	147/100	118
RO 4-1038 + chlorothiazide at 4-6 wk.	37	163/99	120	37	139/93	109
RO 4-1038 at maximum duration	24	181/105	130	25	158/101	120
RO 4-1038 + chlorothiazide at maximum duration	35	175/107	129	35	154/100	118
					Supine	
Chlorothiazide alone				28	179/110	133
RO 4-1038 + chlorothiazide at 4-6 wk.				28	162/99	119
RO 4-1038 + chlorothiazide at maximum duration				28	173/105	127

Matched groups (essential and renal combined)

either RO 4-1038 or chlorothiazide was discontinued. Previous data indicated that RO 4-1038 exerted a maximal hypotensive effect within 3 to 4 weeks of continued administration. Early blood pressure response was therefore arbitrarily selected as the average blood pressure recorded after 4 to 6 weeks of drug therapy at a constant dosage and was then compared to the average blood pressure recorded after maximum duration of therapy (Table I).

Of the 44 patients who received the combination of RO 4-1038 and chlorothiazide only 28 patients received chlorothiazide alone at some time during this study. In a comparison of the hypotensive response to chlorothiazide alone with RO 4-1038 plus chlorothiazide, therefore, the data from the smaller group of 28 patients were matched. Similarly, the blood pressure responses of the 30 patients who received RO 4-1038 alone for extended periods (greater than 3 months) were matched against the control blood pressure responses of this same group. In an analysis of all the other data the blood pressures of the entire group of 53 patients were used as controls. Mean arterial blood pressure was calculated as the diastolic pressure plus one third of the difference between systolic and diastolic values.

The average single daily dose of RO 4-1038 was 13 mg. with a range of 2.5 to 30 mg. Because these were outpatients an attempt was generally not made to increase the dosage of RO 4-1038 to maximally tolerated levels. When patients reported postural faintness, syncope, or other untoward symptoms, the dosage was immediately and permanently reduced. The dose of chlorothiazide was arbitrarily set at 500 mg. twice daily.

Renal						*Total group*	
Supine			*Standing*			*Mean blood pressure (mm. Hg)*	
Number of patients	*Average BP (mm. Hg)*	*Mean BP (mm. Hg)*	*Number of patients*	*Average BP (mm. Hg)*	*Mean BP (mm. Hg)*	*Supine*	*Standing*
12	196/120	145	7	187/124	145	143 ± 16	143 ± 10
11	170/103	125	11	142/93	109	127 ± 23	114 ± 22
9	164/105	125	9	137/92	107	121 ± 16	109 ± 15
7	178/105	129	7	144/96	112	130 ± 19	118 ± 24
9	184/114	137	9	171/107	128	131 ± 19	122 ± 21
	Standing						
28	168/113	131				133 ± 15	131 ± [illegible]
28	139/93	112				119 ± 18	107 ± 18
28	153/101	11				127 ± 18	117 ± 13

The onset of action and length of time necessary for maximum hypotensive effect of RO 4-1038 was ascertained from the data on 14 patients who were started on this drug during hospitalization. The duration of effect after discontinuance of the drug was verified by blood pressure readings taken at home by 9 patients. Duration of therapy ranged from 3 to 22 months, with an average of 13.6 months.

Toxicity studies consisted of the following measurements at frequent intervals: urinalysis, serum creatinine, complete blood count, serum bilirubin, cephalin flocculation, glutamic-oxalacetic transaminase, and Bromsulphalein retention. Urinary tryptamine excretions, the best reported index of over-all MAO inhibition, were determined in 25 patients during the control period and while they received variable doses of RO 4-1038.

Detailed studies of cardiac output, renal hemodynamics, and body fluid spaces were performed on a group of 11 hospitalized patients and were reported elsewhere.[4]

Results

The blood pressure responses are individually tabulated in Table I and summarized in Table II. The statistical data are presented in Table III.

RO 4-1038 given alone. In 44 patients who received an average dose of RO 4-1038 of 13.7 mg. daily for 6 weeks the mean arterial pressure decreased in the supine position from 143 to 127 mm. Hg, a fall of 16 mm. Hg or 11.2 per cent. The mean standing blood pressure decreased by 29 mm. Hg or 20 per cent. Four patients (8 per cent) failed to have any hypotensive response. The decreases in both supine and standing blood pressures are highly significant with

Table III *Statistical significance of data in Table II*

	p	
	Supine	*Standing*
Control vs RO 4-1038 (4-6 wk.)	< .001	< .001
RO 4-1038 vs RO 4-1038 + chlorothiazide (4-6 wk.)	> .05	> .05
RO 4-1038 (4-6 wk.) Supine vs standing	< .01	
RO 4-1038 + chlorothiazide (4-6 wk.) vs chlorothiazide alone	< .01	< .001
RO 4-1038 + chlorothiazide (4-6 wk.) vs RO 4-1038 + chlorothiazide (max.)	> .05	< .05
Control vs RO 4-1038 (max.)	> .05	< .001
Control vs RO 4-1038 + chlorothiazide (max.)	< .01	< .001
RO 4-1038 (max.) vs RO 4-1038 + chlorothiazide (max.)	> .05	> .05

The p values are calculated from the standard t test assuming normal distribution.

a p value of less than 0.001 (Table III). That there is a greater postural effect of the MAO inhibitor however is indicated by a statistically significant difference in mean blood pressures in the standing position versus the supine position at the 4 to 6-week interval ($p < 0.01$).

Blood pressures recorded after RO 4-1038 alone had been continuously administered for a period of 1.5 to 21 months (average, 4.7 months) to 30 of these patients revealed an average decrease in mean arterial pressure of 13 mm. Hg (9.1 per cent) in the supine position and 25 mm. Hg (17.6 per cent) in the upright position. When these pressures are compared to the control blood pressures, the hypotension is statistically significant in both the supine and the standing positions.

The average dose of RO 4-1038 at maximum duration of therapy was 10.8 mg per day. The decrement in blood pressure after the administration of RO 4-1038 commenced in from 3 to 15 days (average 8 days) with the maximal decrease on a constant dosage occurring in from 4 to 22 days (average 14 days). When RO 4-1038 was discontinued the blood pressure started to increase in from 1 to 10 days (average 3 days) and reached its maximum value in 4 to 19 days (average 8 days).

RO 4-1038 given with chlorothiazide The combination of RO 4-1038 and chlorothiazide was given to 44 patients. Only one patient failed to have a hypotensive response. The average dose of RO 4-1038 at the 6-week interval was 12.5 mg daily plus 500 mg of chlorothiazide twice daily. The decrease in mean arterial pressure was 22 mg Hg (15 per cent) in the supine position and 34 mm Hg (23 per cent) in the upright position. When compared to the control blood pressures, these decreases are both highly significant ($p < 0.001$). The further decrement in blood pressure, however obtained by the addition of chlorothiazide to RO 4-1038 was not statistically significant ($p > 0.05$).

Forty four patients received RO 4-1038 plus chlorothiazide for extended periods of 3 to 22 months (average, 10.2 months). The decreases in mean arterial pressure were 12 mm Hg (9 per cent) in the supine position and 21 mm Hg (14.6 per cent) in the upright position. This hypotensive effect is significant ($p < 0.01$) in the supine position and highly significant ($p < 0.001$) in the upright position. The decreased effectiveness of RO 4-1038 plus chlorothiazide at maximum duration as compared to the 6-week period is of questionable statistical significance ($p < 0.05$ supine and < 0.05 standing). The average dosage of RO 4-1038 in this group was 14.8 mg daily.

When the combination of drugs is compared with RO 4-1038 alone at maximum duration it would appear that the addition of chlorothiazide does not cause a more marked hypotensive response than does RO 4-1038 alone. The effect of RO 4-1038 *plus chlorothiazide* at 6 weeks was compared to that of chlorothiazide alone in 28 patients. The RO 4-1038 caused a highly significant further decrease in mean arterial pressure in the standing position ($p < 0.001$) and a significant reduction in supine pressures as well ($p < 0.01$).

Tryptamine excretion Urinary tryptamine excretion was measured in 25 patients before the administration of RO 4-1038 and after 4 to 6 weeks of therapy. The control values fell in the range reported by Oates and Zaltzman. The excretion of tryptamine consistently increased from one

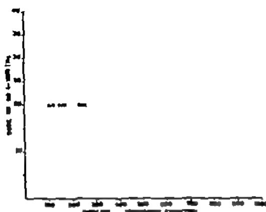


Fig. 1 Relation between dose of RO 4-1038 and urinary tryptamine excretion.

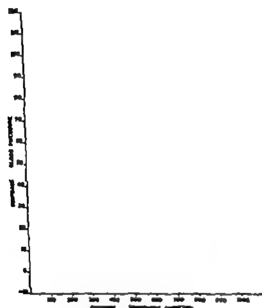


Fig 2 Relation between blood pressure response to RO 4-1038 and urinary tryptamine excretion.

to tenfold Figs. 1 and 2 show the relationship of the percentile increases in tryptamine excretion to drug dosage and hypotensive response respectively The random scatter in the points indicates that there is no correlation between these parameters.

Side effects The adverse and beneficial side effects of RO 4-1038 are listed in Table IV All comments of the patients were listed even when the effects noted could not be definitely attributed to the drug The most prominent side effect was distinct mood elevation this was so constant that many patients were very reluctant to discontinue the medication for any reason With larger doses of the MAO inhibitor the symptom sometimes progressed to nervousness and insomnia. Constipation dry mouth and difficulty in ejaculation symptoms often associated with ganglionic-blocking agents each occurred in approximately one fifth of the patients. It was of interest that in some males a definite progression in sexual side effects occurred with increasing doses in the following order increased libido and potency difficulty with ejaculation difficulty with erection. Some patients experienced increased sweating particularly about the head and neck. An equal number of patients complained of gross twitching of their extremities which was most marked at night while asleep this symptom only occurred in those patients on a high

Table IV Side effects of RO 4-1038 in 54 patients

Side effects	Number of patients		Per cent of total	
Central nervous system	42		78	
Mood elevation		34		62
Nervousness, irritability		10		18
Twitching		9		16
Diminution in headaches		7		13
Insomnia		6		11
Increased appetite		5		9
Psychosis		1		2
Parasympathetic	20		45	
Dry mouth		11		20
Constipation		11		20
Bladder retention		2		4
Sexual	14		26	
Decreased potency		7		13
Difficulty in ejaculation		6		11
Increased potency		5		9
Other	14		26	
Increased diaphoresis		9		16
Visual disturbances		6		11
Decreased anginal pain		3		6
Nasal congestion		2		4
Tingling of hands		2		4
Weakness or numbness of legs		2		4
Skin rash		2		4

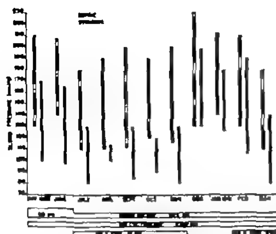


Fig. 3. Additional effect of RO 4-1038 when combined with other hypotensive drugs in a patient with accelerated hypertension. Note (1) the decrease in dosage of guanethidine from 150 mg. to 62.5 mg. daily when RO 4-1038 was added, and (2) the increase and subsequent decrease in blood pressure during discontinuation and reinstitution of RO 4-1038.

dosage of RO 4-1038 usually 20 mg. daily or greater. Because of reported impairment in red-green color discrimination after the use of Catron, the majority of subjects were tested before and during therapy for color discrimination by the pseudo-isochromatic test; in no instance was there any abnormality.

Toxicity. In the discussion of toxicity our total experience with RO 4-1038 is included, i.e., patients are included who were excluded from the present study for various reasons. The observations represent, therefore, approximately 14,000 patient-days of therapy. One patient developed an acute paranoid delusional *psychosis which disappeared within a few* days after discontinuation of the drug. It was thought that the clinical course and the results of the psychological tests were suggestive of a toxic psychosis. One patient, a young Japanese woman, developed severe hepatitis which required therapy with glucocorticoids. She had been receiving RO 4-1038 for 7 weeks and her dose had been increased to 15 mg. daily 1 week before the onset of the hepatitis. It is thought that she probably had infectious hepatitis unrelated to the RO 4-1038 on the evidence that her uncle, whom she seldom saw but who attended a family picnic with her about 60 days before the onset of her hepatitis, developed hepatitis 2 weeks before she did. She is now completely recovered. Nine patients who had received or were receiving RO 4-1038 died during the period of study. Of these, 4 were examined post mortem. In all except one death was attributable to causes definitely unrelated to drug therapy; this patient died of a sudden cardiac arrhythmia of unknown cause. At autopsy he had little except severe left ventricular hypertrophy secondary to advanced hypertension. He had received up to 50 mg. of RO 4-1038 daily, but the drug had been withdrawn 2 weeks prior to his death. Careful post*mortem studies in these patients failed to* disclose any significant liver pathology.

Serial studies of the blood and urine failed to demonstrate any abnormalities of the renal, hepatic, or hematopoietic systems.

Discussion

The foregoing data confirm preliminary observations that the MAO inhibitor RO 4-1038 is a potent oral hypotensive agent in both essential and renal hypertension. Although its effect is primarily postural, there is also a highly significant decline in supine blood pressure at 6 weeks. It is to be noted, however, that with prolonged therapy the decrease in blood pressure is less than at the 6-week interval. It is not clear whether these changes indicate tolerance to the drug for the following reasons: (1) As noted previously, when patients exhibited postural faintness or other untoward symptoms during the early period of drug therapy, the dosage *was reduced and no further effort was* made subsequently to increase it to maximally tolerated (or maximally hypotensive) levels. Pertinent in this regard may be the average dose of 10.8 mg. daily at the period of maximum duration compared with 13.7 mg. daily at the 6-week period. (2) It is a reasonable assumption from the natural history of untreated hypertension that some of the patients had a worsening (increase) of their hypertension during the period of therapy. Thus, the control blood pressures taken as much as 22 months prior to the figures recorded after maximum duration of therapy would be invalid and

the data would be skewed accordingly. Conversely, it is unreasonable to assume that the blood pressures in any significant proportion of this group of patients with moderately severe hypertension would have improved spontaneously. (3) In individual patients, the blood pressure generally increased promptly (Fig. 3) when RO 4-1038 was discontinued after variable periods of time. It was the impression of the physicians, however, that in some instances tolerance (or a spontaneous worsening of the hypertension) did occur. It can only be stated that this was not usually the case. Unfortunately, since most of the recent clinical reports in the literature on the use of MAO inhibitors in hypertension are limited to relatively brief periods of therapy,[7-16] there are no comparable data with regard to other related compounds, although it has been stated that acquired tolerance to the hypotensive effects of iproniazid was not observed in a small group of patients over a period of 8 months.

The present data are in disagreement with those of other reports on the hypotensive effects of MAO inhibitors[12-14] as well as with our own preliminary observations, in that the addition of chlorothiazide did not cause a significant further reduction in arterial pressure. This surprising lack of potentiation in patients who were receiving prolonged therapy with the combined drugs (RO 4-1038 plus chlorothiazide) may be partially explained by the assumption that this group generally had more severe (and progressive) hypertension than did the group given RO 4-1038 alone and that the spontaneous worsening of the hypertension nullified the hypotensive effects of the chlorothiazide. This explanation, however, cannot be applied to the early (4 to 6-week) results. Since in some patients there did appear to be an additive effect of the two drugs, a larger sample series must be studied in order to validate this conclusion.

It is of interest that the lack of potentiation by chlorothiazide was confirmed in a smaller group of hospitalized patients on whom hemodynamic data were obtained. The intake of sodium generally was not restricted in any of the hospitalized patients, and all determinations were made after at least 4 to 6 weeks of administration of chlorothiazide. Since there was no reduction in cardiac output, plasma volume, total exchangeable sodium, or sodium space in these patients, the early hypotensive action of chlorothiazide which has been attributed by some investigators to the depletion of plasma volume secondary to natriuresis[8, 14] could not have been present. The long term effects of chlorothiazide on the reduction of blood pressure are still poorly documented or understood.[1, 20, 26]

We have used RO 4-1038 concomitantly with other hypotensive drugs, including ganglionic-blocking agents in some patients with more severe hypertension. The data are insufficient for analysis, but there appears to be a substantial additive effect in at least one half of these patients (Fig. 3). The dosage of RO 4-1038 was increased to 50 mg. daily in a few patients who had very severe or accelerated hypertension without any further hypotensive effect. In general, there appears to be a flat dose response curve above approximately 20 mg. daily, i.e., the hypotensive response is seldom increased significantly above this dose level.

Although several recent reports have appeared on the use of other MAO inhibitors in hypertension, insufficient raw data are presented to permit a direct comparison with RO 4-1038, particularly with regard to long-term effects. It can only be stated, therefore, that (1) all MAO inhibitors studied appear to have *some* hypotensive effect in man[27] and (2) on a milligram basis, RO 4-1038 appears to be more effective than iproniazid or phenipraxine in reducing blood pressure.

Generally, the side effects of RO 4-1038 were mild (Table IV) and seldom necessitated cessation of therapy. With rare exceptions the over-all patient acceptance was enthusiastic. There was a rough correlation between dosage and side effects with considerable individuality of the patients. Increased nervousness, for example, and difficulty in ejaculation were fairly common at doses greater than 20 mg. daily. In the usual therapeutic dose, however, the main side effect was mood elevation. Although the postural hypotension suggests a sympatholytic action

in contrast to the ganglionic blocking agents very few effects of parasympathetic blockade were evident. Toxicity studies failed to demonstrate renal hepatic central nervous-system or hematopoietic toxicity One patient developed hepatitis but this could not be definitely attributed to the drug

It is of interest that in agreement with Gillespie and associates, no correlation was found between the increase in urinary tryptamine excretion and the hypotensive response in individual patients. This is in accord with the view that the antihypertensive effects of RO 4-1038 and related compounds may be unrelated to their MAO inhibiting properties.

On the basis of these observations, we believe that the MAO inhibitor RO 4-1038 is a valuable adjunct in the treatment of hypertension In our experience when given alone it appears to be more potent than either reserpine or chlorothiazide but less potent than the ganglionic-blocking agents. It probably is indicated primarily in mild or moderate hypertension but can be used with other agents including ganglionic blockers, in more severe hypertension Because of its cumulative effect it is suggested that the usual starting dose should be 5 mg daily with 5 mg increments at 2 week intervals to a maximum of 20 mg daily It is further suggested that in some instances chlorothiazide may potentiate its hypotensive action.

Summary

1 The long term effects of a typical monoamine oxidase inhibitor DL-serine N[2] isopropylhydrazide monohydrochloride (RO 4-1038) alone or in combination with chlorothiazide were studied in 53 patients with moderate arterial hypertension

2. There was a highly significant decrease in mean arterial pressure in both the supine and standing positions after 6 weeks of therapy with a more marked response in the standing position After prolonged administration the hypotension was still significant The addition of chlorothiazide did not appear to cause a significant further reduction in blood pressure.

3 Side effects of RO 4 1038 were mild and seldom necessitated discontinuation of therapy No major toxicity was found.

4. No correlation was found between the increase in urinary tryptamine excretion and the hypotensive response in individual patients, which suggests that the antihypertensive effects of RO 4-1038 and similar compounds may be unrelated to their MAO inhibiting properties

5 It is thought that RO 4-1038 is a valuable adjunct in the treatment of hypertension

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Observations on the cardiovascular involvement in Friedreich's ataxia

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Patients with Friedreich's ataxia commonly develop cardiac disease and some of them die of it. How this relates to the neurological pathology is unclear, nor is it apparent how the heart becomes involved. Theories on the etiology of the cardiac pathology in Friedreich's ataxia have included attribution of it to the musculoskeletal deformities, congenital disease, coronary artery involvement, cardiac effects of involvement of the central nervous system, and the simultaneous effect on heart and nervous system of a heritable biochemical trait. All these theories have been challenged and their separate merits discussed in several modern reviews.[1-4]

Necropsy studies of persons who died of Friedreich's ataxia, particularly of those with cardiac involvement, have been uncommon and have not yet resolved the question of the etiology of the heart disease. Recently we had the opportunity to observe a 19-year-old man with Friedreich's ataxia who not only died of congestive heart failure, but who also had intractable atrial arrhythmias which materially contributed to his myocardial insufficiency. A careful study of his heart and blood vessels at necropsy revealed a striking involvement of small arteries, most particularly in the heart and lungs. Study of the heart included subserial sectioning of the sinus node and A-V (atrioventricular) node.

Case report

This young white man was first seen at the Indiana University Medical Center in 1957 at the age of 15 years because of ataxia. On physical examination then there was an ataxic gait with minimal spastic element, and a classic Friedreich's deformity of the feet, which were short with a high arch and exhibited dorsiflexion.

His past medical history and a review of systems were not contributory. Family history disclosed that the patient's father died of a coronary thrombosis, but the mother was living and well. Of 3 siblings, 2 were well but a sister had classic Friedreich's ataxia.

The next visit was in 1959, at which time he complained of progression of ataxic symptoms, which were described by the attending physician as being rather severe. On examination of the eyegrounds there was temporal pallor of both discs, bordering on atrophy. No mention of any cardiovascular abnormality was made in 1957 or 1959. He was seen next on Oct. 24, 1961, because of malaise, shortness of breath, orthopnea, and severe coughing which had been present for approximately 1 month. Because the patient failed to respond to treatment, he was admitted to the Medical Center for further care.

On physical examination the blood pressure was 130/80 mm. Hg and the pulse was regular at 80 per minute with a few premature contractions. The temperature was 100.4°F rectally. The

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patient was well oriented at the time of admission, cooperative, and in no acute distress. Neuromuscular examination revealed the previously described findings of Friedreich's ataxia. The heart was enlarged to the left, with cardiac dullness extending past the mid-clavicular line. The first sound at the apex was of good quality; the second pulmonic sound was louder than the second aortic sound. In the pulmonic area the second sound split normally on inspiration. An early diastolic third heart sound was heard at the apex. A Grade 3 (of 1 to 6), high-pitched pansystolic murmur was present at the mitral area. The chest was clear to auscultation and percussion, and there were no peripheral signs of heart failure. The remainder of the examination was not contributory.

Laboratory studies including serology, complete blood count, urine examination, serum bilirubin, protein-bound iodine, total protein and A/G ratio, electrolytes, fasting blood sugar, oxalacetic transaminase, thymol turbidity, blood urea nitrogen, prothrombin time, alkaline phosphatase, antistreptolysin-O titer, C-reactive protein, and three blood cultures were all normal or negative.

On fluoroscopic examination of the chest there was marked generalized enlargement of the heart. Pulmonary vascular markings were normal and the lungs appeared to be clear. An electrocardiogram (Fig. 1) showed normal sinus rhythm with atrial and ventricular premature beats. Right axis deviation was present with some slurring of the QRS complexes suggestive of intraventricular conduction defect, especially in Lead V

He was discharged after 11 days, only to be readmitted on Jan. 4, 1962, because of recurrence and progression of dyspnea, weakness, and orthopnea. On physical examination there was now a respiratory rate of 24, a pulse rate of 124 per minute with occasional premature beats, and a blood pressure of 120/95 mm. Hg. Other cardiovascular findings were similar to those described during his first hospital admission, although the diastolic gallop was much more pronounced. Again the chest was clear to auscultation and percussion, and there were no peripheral signs of congestive heart failure.

Shortly after admission to the hospital he developed tachycardia, nausea, vomiting, and abdominal discomfort. An electrocardiogram taken on the third hospital day (Fig. 2) showed atrial fibrillation with multifocal ventricular premature beats. The chest x-ray film revealed some fluid in the right pleural cavity. Both lung fields showed massive congestion when compared with the study done 9 weeks previously, and there was a definite and rather striking increase in the size of the heart.

On the fourth hospital day the patient was found to have an apical rate of 160, and the electrocardiogram now showed atrial flutter with 2:1 response (Fig. 3). The arrhythmia failed to respond to either quinidine or digitalis, and the patient died quietly on the fifth hospital day.

Necropsy disclosed a marked scoliosis of the dorsolumbar spine and bilateral pes cavus. Multiple infarcts were present in the lungs. The liver and spleen were congested, and weighed 1,850 and 282 grams, respectively.

On gross examination the heart weighed 550 grams and the surface was opaque white, due to thickening of the pericardium. There were no pericardial adhesions, and the white surface was smooth. Individual chambers were about equally enlarged and hypertrophied; the right and left ventricles were 8 and 16 mm. thick, respectively. The left atrium was not disproportionately enlarged. The septa were intact and all the cardiac valves were normal.

The right coronary artery supplied the sinus node branch at the usual site of origin[8] and continued beyond to cross the crux of the heart and supply the A-V node and half of the posterior surface of the left ventricle. It was patent throughout its course and had no atheroma. The left coronary artery bifurcated in the usual fashion, with the left circumflex branch terminating at the obtuse margin of the heart; there were no lesions in the left circumflex ramus. Two centimeters from its origin a primary branch of the left anterior descending coronary artery was 60 per cent compromised by an old atheroma, but the remaining lumen was free; this luminal encroachment is estimated in the fixed state and may or may not correspond to similar encroachment while the patient lived. Streaky fibrosis was present throughout both the right and left ventricular myocardium and was no more common in the area supplied by the left anterior descending artery than elsewhere.

On gross examination the regions of the sinus node and A-V node were not remarkable. Sections of the nodes were made at intervals of 2 mm. in a manner described previously. In addition, 7 samples of the left ventricle and interventricular septum, 4 of the free wall of the right ventricle, 4 of the left atrium, 2 of the aorta, and 2 of the main pulmonary artery were examined. Selected sections of all three coronary trunks, including the atheroma in the left anterior descending artery, were examined. Other samples of tissue in which the arteries were studied microscopically included brain, spinal cord, stomach, small intestine, esophagus, parathyroid, pancreas, skin and skeletal muscle, testes, prostate, bone, adrenal, kidney, liver, spleen, and lung.

The pericardium was thickened by collagen, with very little cellular reaction in the epicardium. There was more thickening in some regions than in others, but the surfaces of all four chambers were involved. The aorta and pulmonary artery were normal, although a few of their vasa vasorum were diseased by a process similar to that in the myocardial arteries. All the arteries examined in the tissues listed above, except the heart and lungs, were normal. For most other tissues, however, there was only one specimen to examine.

Throughout the myocardium of all four chambers there were areas of fibrosis which varied in size, some representing coalescence of several foci. In addition, there were regions of focal degeneration of myocardial fibers, with a small amount of focal cellular infiltration, largely lymphocytes; there were no unusual numbers of eosinophils nor neutrophils, and only rare mast cells, which were always located near small blood vessels, as they normally are. Myocardial fibers did not vary in size more than they normally do. Purkinje fibers as usual

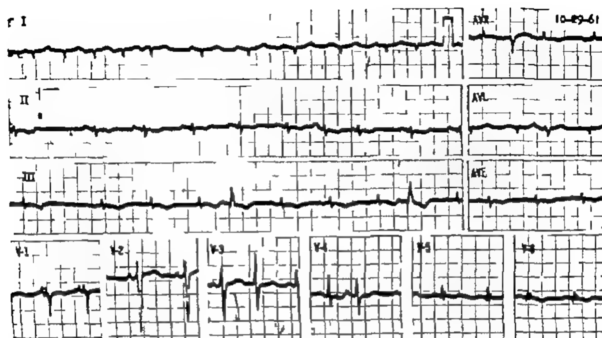


Fig. 1. T el lead electrocardiogram made Oct. 29 1961. Basically a sinus rhythm and normal A-V conduction. See text for other description.

Fig. 2. Strips of Lead V electrocardiogram made 2 day (*upper two strips*) and 1 day (*lower 3 strips*) prior t death. This intractable trial arrhythmia was a major factor in the progressi ely increasing cardiac failure.

being larger. However there was great variation in both the size and the density of nuclei, which were more pronounced in some regions than in others, and particularly so surrounding areas of fiber degeneration. This nuclear pleomorphism (Fig. 3), noted also by Russell, is commonly observed with protracted focal ischemia, as occurs, for example in some cases of myocardial infarction due to coronary atherosclerosis.

Small arteries, mostly in the 100 to 300 micra range (but some up to 1.0 mm. in diameter), were extensively diseased throughout the heart and lungs (Figs. 4-7). In the heart the arterial histopathology was in the following forms: (1) degeneration of the tunica media, either with or without formation of small cysts (2) intimal hyperplasia (3) amorphous endothelial deposits which were usually (but not always) Schiff positive but did not stain with PTAH (phosphotungstic acid hematoxylin) and Congo red, and did not fluoresce with thioflavine orange. Some arteries had only one of these abnormalities, whereas others had all three. Diseased arteries were apparent in almost every area examined, but there were also some normal-appearing arteries. Because of the extensive involvement, it seems likely that all the arteries were focally diseased, even when normal in appearance in any single given section; serial sections were not made to determine this point, however.

A few larger myocardial arteries were similarly diseased, including one major branch of the left anterior descending coronary artery which was 1.5 mm. in diameter. The great majority of the larger arteries were normal to gross and microscopic examination, however, a point of importance concerning previous conflicting observations in regard to the coronary arteries in hearts of patients who died with Friedreich's ataxia (see Discussion). Both the sinus node and A-V node arteries, each 0.7 to 1.0 mm. in diameter in most of their course were involved.

In the lungs the majority of arteries which were 100 to 300 micra in diameter were diseased, including several small pulmonary emboli (Fig. 7). The pathology in the small pulmonary arteries was predominantly intimal proliferation, with some degeneration in the tunica media, but some arteries had lamellar hyperplasia of the endothelium rather than radial proliferation.

Many of the sinus node fibers were degenerating, some showing the same nuclear pleomorphism apparent in the rest of the heart (Fig. 8). There were a few similar foci in the A-V node but much less extensive than in the sinus node. Near the sinus node there were also some parasympathetic ganglia with both hemorrhage and degeneration, possibly ischemic in origin. The pericarditis over the sinus node (in essence almost an epicardial structure[4]) also involved some juxtanodal ganglia.

Discussion

In this case there seems little doubt that the cause of the heart disease was extensive pathology of the smaller coronary arteries. This is not only a logical explanation for the widespread focal degeneration and fibrosis in the myocardium but also for the clinically important atrial arrhythmia, since the same arterial pathology involved the sinus node.

The question then naturally arises whether this is an unusual case of cardiac disease in a patient with Friedreich's ataxia or whether coronary artery pathology is the principal or sole explanation for the pathology of the heart in these patients. Although involvement of the coronary arter-

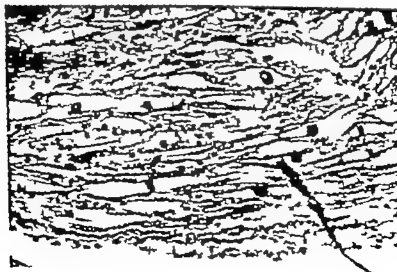


Fig. 3. Marked nuclear pleomorphism is shown by these Purkinje fibers of the left ventricle. Goldner trichrome stain, ×190.

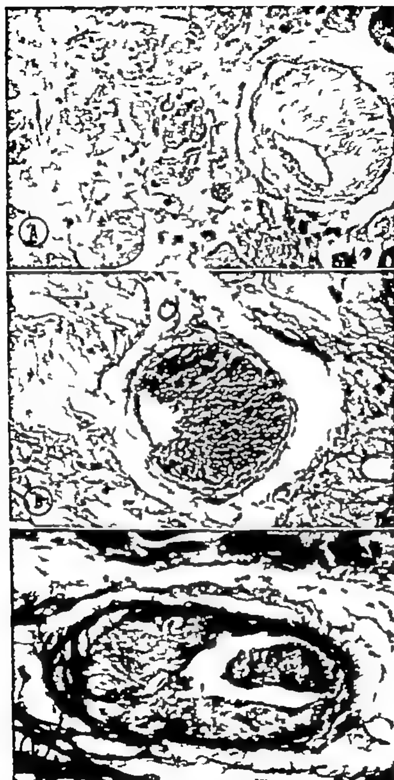


Fig. 4. Obliterated small arteries in the myocardium of the left (*A* and *B*) and right (*C*) ventricles. The histologic detail is identical to that of the arteries illustrated by Nadas and associates. In all three of these photomicrographs the luminal encroachment is due to an amorphous endothelial deposit which is Schiff positive. *A* stained with Goldner trichrome, ×190; *B* with periodic-acid Schiff (PAS), ×190; *C* with Verhoeff Van Gieson elastic, ×315.

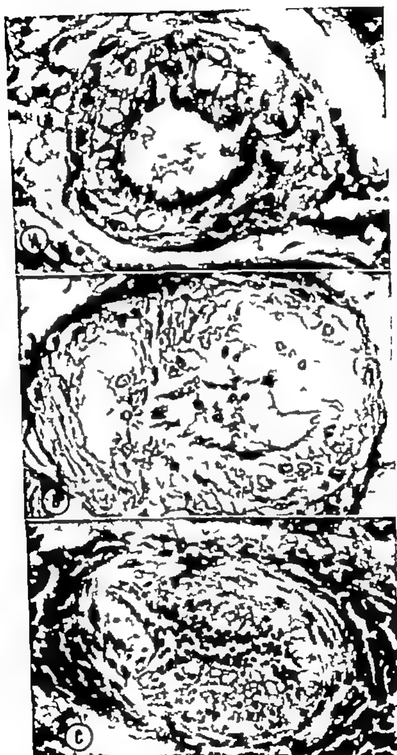


Fig. 5. Further illustration of the spectrum of arteriopathy in three arteries in the right atrium. In *A* there is cystic degeneration of the tunica media. The medial degeneration in *B* is also focal but gelatinous, the gel failing to stain with PAS, PTAH, Congo red, and acridine orange. In *C* there is some medial degeneration but predominantly endothelial proliferation. It seems likely that all these processes are related and that the medial degeneration is the original event. *A* stained with PAS, ×480; *B* with Goldner trichrome, ×480; *C* with Goldner trichrome, ×315.

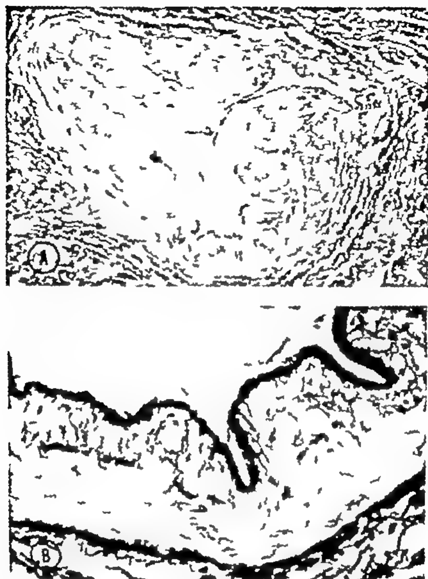


Fig. 6. Two sections of sinus node artery taken 2 mm. from each other. In *A* there is thin tunica media and considerable endothelial proliferation (Goldner trichrome ×120). In *B* the details of cystic medial degeneration between the internal and external elastic laminae are shown (Verhoeff-Van Gieson ×480).

ses has for some time been suggested for this explanation most recent reviewers of the question have rejected it primarily for the three following reasons (1) Several reports described myocardial damage but "normal" coronary arteries.[19-21] (2) In two instances postmortem coronary angiograms were said to be normal.[21] (3) Electrocardiographic evidence of myocardial infarction has not been present although many other electrocardiographic changes have occurred.[1] There is one flaw which may invalidate all three of these reasons for rejection of coronary disease as the cause of the cardiac pathology in Friedreich's ataxia and that concerns the size of artery suspected.

If one is suspecting pathology of the larger coronary arteries, then conventional electrocardiographic evidence for myocardial infarction should have been observed if the large arteries were sufficiently involved. Similarly postmortem coronary angiograms should be abnormal if larger arteries are involved but not necessarily if it is only the small vessels. As a matter

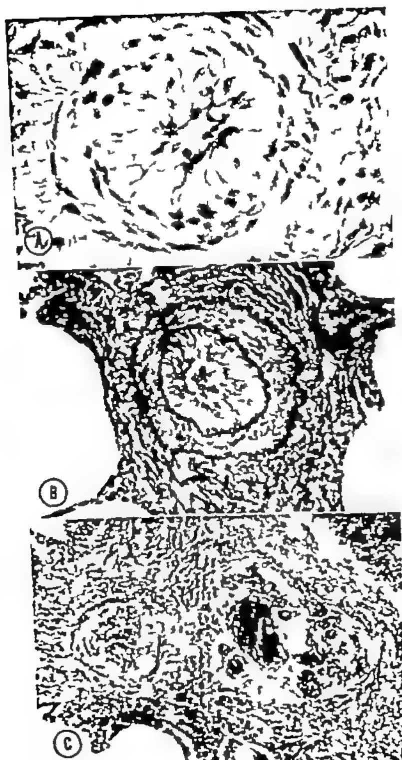


Fig. 7. The typical histopathology of the smaller pulmonary arteries is shown. Details of the medial degeneration are shown best in A (Goldner stain, ×480) along with the occlusive endothelial proliferation. Note the radial pattern of the endothelial proliferation. In *B* (Verhoeff Van Gieson, ×190) the relationship of the endothelial proliferation and medial degeneration to the elastic laminae is illustrated. In *C* a glomus lesion is shown adjacent to a diseased artery in the lung, suggesting that there has been severe and long-standing pulmonary hypertension (Goldner trichrome, ×120).



Fig. 4. Degeneration of fibers in the sinus node is shown in *A* (Goldner trichrome, ×480); note the nuclear pleomorphism and pyknosis. Similar degeneration is present among fibers of the A-V node in *B* (Goldner trichrome, ×480).

of fact the angiogram in at least one of the frequently cited cases[17] does show suspicious narrowing in the terminal portions. Concerning the reports of normal coronary arteries in hearts with myocardial damage, none of these examiners has made special mention of the smaller vessels, and it is not unreasonable to assume that their descriptions refer to those coronary arteries conventionally studied in a routine necropsy, which are the major arteries. If only those arteries were considered in the present case, for example, the single atheroma in a branch of the left anterior descending coronary artery would be the sole lesion and its significance could be dismissed on the absence of localized infarction in the region it supplied. The argument that the youth of most patients who have cardiac involvement from Friedreich's ataxia is against coronary disease as the etiology[4] may be dimissed on the basis that the arteriopathy is distinctly not ordinary atherosclerosis. Thus, all the arguments previously marshalled against coronary disease in Friedreich's ataxia are not so strong as they initially seem.

Presuming that the smaller coronary

arteries are the principal cardiac pathology, is there any feature of the cardiac disease which they fail to explain? Certainly the focal fibrosis and degeneration commonly indicated as the "myocarditis" of Friedreich's ataxia could easily be due to progressive obliteration of these small arteries. So could the bouts of atrial arrhythmias[4b, 7] as well as the heart block, Stokes-Adams attacks, and sudden death[4a, 11] since the arteries in the sinus node and A-V node are just the size to be included in the involvement of small vessels. With the recurring ischemic degeneration of very small areas of myocardium the only foci likely to attract clinical attention are those which involve either the sinus node or A-V node, all others simply leading to more and more focal fibrosis and gradually increasing myocardial insufficiency until the point at which the loss of only a small additional amount of myocardium or the sudden addition of a taxing myocardial load—such as a rapid atrial arrhythmia or heart block—leads to quickly increasing intractable cardiac failure.

The pathologic sequence may be summarized as follows. As more and more small arteries are obliterated, the volume of damaged myocardium increases, cardiac output and coronary perfusion pressure decrease, and ultimately flow through narrowed but nonoccluded small arteries also becomes inadequate. Thus, the increasing fibrosis makes small arteries with less and less luminal encroachment just as much a liability as were completely occluded ones originally. In addition, the failing myocardium renders transanastomotic flow poorer, and all the factors simply compound themselves.

If the gradual death of very small foci of myocardium does not ordinarily accelerate, then there is little reason to anticipate that chemical evidence of myocardial necrosis will be found. And since the injury is diffuse rather than localized in one area of myocardium, the only electrocardiographic change to be expected would be the nonspecific one commonly seen with such processes, which consists of generalized T wave inversion without much loss of QRS voltage. Chronic myocardial degeneration will be liberating myocardial antigen into the circulation, however, and it is possible that the pericarditis represents autosensitization to this.

To our knowledge, the pathology of the pulmonary arteries has not previously been described in Friedreich's ataxia, although numerous cursory summaries of necropsy findings have included examination of the lungs. Bronchopneumonia, atelectasis, and pulmonary congestion have been the principal previous findings. Because some emboli were present in the smaller arteries in this patient, the possibility must be considered that multiple small emboli were the cause of all the pulmonary vascular pathology, since similar lesions have been produced experimentally with emboli.[19] Several points suggest that emboli are not the only explanation for the pulmonary vascular pathology, however, although they may have contributed to it. The most cogent of these is the fact that the same size artery is involved in both the heart and the lungs. Coexistent pathology of arteries of this size in both the heart and the lungs has been observed in several other diseases with increased familial incidence.[21-23] Additionally, the predominant lesion in the pulmonary arteries was one of radial intimal proliferation, which Brenner[4] has suggested is more often a primary pathologic change than is the lamellar intimal hyperplasia. Finally, in one of the earliest reports of cardiovascular pathology in Friedreich's ataxia, Pitt carefully described extensive obliterative "endarteritis" of the upper extremities (although he failed to describe the coronary arteries) and on the basis of this arteriopathy and other points he suggested that Friedreich's ataxia was a systemic disease rather than exclusively one of the central nervous system.

The pulmonary vascular pathology may be of considerable significance. If it is extensive, as in the present case, it may sufficiently compromise blood flow through the lungs and return to the left heart so that cardiac output must fall. At the same time this happens, pressures in the right heart must rise, especially during exertion (with fixed pulmonary vascular resistance). Under these circumstances, the right atrial pressure may also rise transiently, reducing effective coronary perfusion pressure[2]

by resisting emptying of the coronary venous system. Since rising right atrial pressure would likely occur at the same time that cardiac output falls, there would then be simultaneous reduction in coronary filling pressure and increase in resistance to coronary emptying.

It now becomes of interest to know the pressures in the right heart in patients with Friedreich's ataxia. One reported examination is listed as normal (Case 18 of Boyer and associates[1]). That pulmonary hypertension may be a more common finding than was previously suspected, however, is supported by the careful physical examinations made by Lorenz and associates[3] of 5 siblings with Friedreich's ataxia and both their parents. All the children and the mother not only had a second pulmonic sound louder than the second aortic sound, but on x-ray examination all 6 also had slight to moderate prominence of the pulmonary artery. The father had neither a loud pulmonic second sound nor prominent pulmonary artery. Of further interest is the fact that Pitt's patient [9] with Friedreich's ataxia also had an accentuated pulmonic second sound. Against the advisability of indiscriminate cardiac catheterization, however, is the lack of documented evidence of pulmonary hypertension in most reported cases, as well as the tendency of patients with cardiac disease and Friedreich's ataxia to sudden death. Cardiac catheterization is known to be hazardous, for example, in so-called primary pulmonary hypertension,[22] another disease in which the small vessels of both the heart and lungs are involved.[23]

On the basis of findings in our case plus the critical assessment of previous necropsy findings in the heart of patients with this disease, it is suggested that pathology in the smaller coronary arteries is responsible for the cardiopathy in Friedreich's ataxia. If there is any "toxin"[4] involved, it may be antigens liberated by the degenerating myocardium which, by autoimmunization in turn, may account for the pericardial thickening so often seen. Disease in the nutrient arteries of the sinus node and A-V node is probably responsible for the atrial arrhythmias and heart block with sudden death which have frequently been reported. Relentlessly progressive myocardial degeneration and fibrosis due to obliteration of the small arteries, or insufficient flow through the narrowed ones when cardiac output falls, is probably responsible for the ultimate cardiac failure. Ischemic damage to cardiac autonomic ganglia may contribute to the disturbances in rhythm and conduction.

One can only conjecture on the etiology of the pathology involving the little arteries in the heart and lungs. It seems reasonable to suspect that this arteriopathy, like the nervous system disease, is also a heritable feature and that the two traits coexist. Whether their coexistence is causally related is unknown. At present it seems unlikely that the pathology of the central nervous system is also due to vascular disease with ischemic degeneration, although this possibility remains to be excluded.

Summary

The case of a young man with Friedreich's ataxia who died of intractable atrial arrhythmias and cardiac failure is presented. At necropsy there was widespread involvement of the small arteries of the myocardium (including the cardiac conduction system) and lungs. After critical review of previous necropsy studies in this disease, it is suggested that the most likely explanation for the cardiopathy of Friedreich's ataxia is obliteration of the small coronary arteries. Potential significance of the pulmonary arteriopathy is briefly discussed.

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The variability of blood pressure: Basal and casual measurements in adult twins

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The complex of influences which affect the measurement of blood pressure constitutes a critical problem in both the clinical and genetic interpretation of this variable. Recognition of this problem has led to the use of standardized procedures which reduce the effects of spurious influences upon blood pressure measurements.[1] Other influences, such as time of day or the conditions of study, also affect blood pressure readings and invariably differ to some extent from study to study. Our purpose is to evaluate the effect which these influences may have upon the genetic interpretation of blood pressure measurements.

The study sample

The study subjects consist of 53 pairs of twins for whom basal[2] as well as casual blood pressure readings were obtained. There were 14 male and 20 female monozygotic (MZ) pairs, and 5 male and 14 female like-sex dizygotic (DZ) pairs. All subjects were over 18 years of age, with a mean age of 25.4 years for males and 29.5 years for females. All subjects were judged to be in good general health on the basis of health history, medical examination, and laboratory workup. The diagnosis of zygosity was based on extensive serologies and other observations. The methods employed in the diagnosis of zygosity and the physical and socioeconomic description of these subjects have been presented in detail.[3]

Methods

Standardized casual blood pressures were obtained for the twin subjects employed in a study of basal blood pressure. In the basal studies the subjects came to the laboratory fasting, and every effort was made to maintain a basal state during the entire study procedure. The manner in which the basal pressure readings were obtained has been presented previously.[2]

The casual blood pressure readings were obtained at the time of the medical examination.[3,4] These readings were taken on the two members of a given pair of twins within approximately 1 hour's time, and by the same examining physician. All casual pressures were taken using a mercury sphygmomanometer, with the subject supine after a short period of rest. Readings were taken routinely on the right arm; this was governed by the position of the examining table. In a number of instances, readings

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were obtained also on the left arm of both members of a pair of twins. The majority of examinations were performed in the evening and in all cases these readings departed considerably from the early morning readings obtained for the basal studies. Comparison of casual and basal blood pressures approximates a measure of diurnal variation and will be referred to as such for the purpose of this report.

The statistical treatment of the casual pressure readings is comparable to that employed for the basal studies. The differences between the two members of the pairs of twins are expressed as mean intrapair variances, in which the mean intrapair variance is $\Sigma x^2/2n$ where x is the difference between the two members of a pair of twins and n is equal to the number of pairs of twins. In individual diurnal variance, x is the difference between the casual and basal readings; in individual left-right variance, x is the difference between readings taken on the left and right arms. In both instances, n is equal to the number of pairs of readings employed in the analysis. The mean interpair variance which estimates the differences between unrelated pairs of individuals in the study population is $s^2 = [\Sigma x^2 - (\Sigma x)^2/n]/n - 1$. In this instance, x is calculated from the average of the values for the two members of each pair of twins, and n is the number of pairs of twins. These variances are multiplied by two to make them comparable to the mean intrapair variances.[2]

The F distribution is used to obtain the probability level of the ratios of the different mean intrapair variances and of the intrapair and interpair variances. In the comparison of monozygotic and dizygotic mean intrapair variances and intrapair and interpair variances a one-tail test of significance will be given; when comparisons between the sexes are made, a two-tail test is required. To obtain the probability level of the ratios of variances calculated from correlated pressure readings, as for readings taken on the left and right arms, and basal and casual pressures of the same individual, Student's distribution is used employing the statistic given by Walker and Lev[4]

$$t = (s_1^2 - s_2^2)\sqrt{N-2}$$

In the interpretation of the correlations of systolic and diastolic pressure the method suggested by R. A. Fisher[3] (pages 195 and 201) is followed.

The comparability of the statistical treatment of the basal and casual pressure readings, and the fact that the method employed is based upon paired blood pressure readings make it possible to (a) perform an analysis of the casual pressure measurements comparable to that carried out with basal pressure measurements[2] (b) determine the magnitude of left-right arm differences (c) compare left-right arm differences between basal and casual readings (d) compare the intrapair variances of basal and casual readings and (e) compare the association of selected variables with basal blood pressure measurements to the association of these variables with casual blood pressure measurements.

Results

The ranges, means, and standard deviations for systolic and diastolic pressures are given separately for males and females and for the left and right arms (Table I). (These values, based upon one member of a pair of twins taken at random, are for the same individuals used in the calculation of the corresponding basal values.[2]) The smaller number of readings on the left arm results from the fact that only readings on the right arm were taken routinely.

The statistical means of the systolic and diastolic pressures do not differ significantly between right and left arms in either males or females, nor does diastolic pressure differ significantly between males and females. When systolic pressure is taken on the right arm the mean pressure for males is significantly greater than that for females (P = .02). When the means of the basal systolic and diastolic pressures (Table I) are compared to the respective means of the casual pressure, it is found that diastolic pressure is essentially unchanged whereas systolic pressure taken casually is significantly greater than that taken basally in both males and females. This is true whether comparison is made with casual pressure readings on the right arm or those on the left arm (P values range

Table I Ranges averages and standard deviations of casual blood pressure measurements for selected individuals

	Males				Females			
		Range	Mean	S.D	n	Range	Mean	S D
Right arm								
Systolic pressure	19	112 150	126 32	11 31	34	90–154	118 12	12 81
Diastolic pressure	19	56–98	77 37	10 50	34	50–78	73 71	10 29
Left arm								
Systolic pressure	14	110–134	121 50	7 20	7	105–148	120 14	15 77
Diastolic pressure	14	60–92	73 93	8 45	7	56–90	74 00	11 08

*These are the same individuals utilized in the basal calculations

Table II Left and right arm measurements and diurnal differences in individuals

Comparison	Males				Females			
		Variance	t	P†	n	Variance	t*	P†
Systolic pressure								
Diurnal Left Left	16	61 81			11	64 95		
			2 25	> 02			3 57	> 005
Casual Left Right	16	23 47			11	15 86		
			5 21	< 001			6 34	< 001
Diurnal Left Right	16	117 72			11	104 73		
Diastolic pressure								
Diurnal Left Left	16	36 [illegible]			11	63 91		
			3 96	< 002			1 47	< 10
Casual Left Right	16	9 81			11	25 50		
			5 11	< 001			2 91	< 02
Diurnal Left Right	16	44 [illegible]			11	94 95		

*The t is obtained using the two variances and correlations between the readings according to the formula given by Walker and Lev
†The greater than (>) or less than (<) sign is applied to the nearest percentage point given by Pearson and Hartley[?] 0 10, 0 05 0 02, 0 01 0 005 0 001

equivalent to the means of the differences between the casual pressures on the left and right arms, are compared to the mean diurnal variances in the same individuals using both left and right arms (Table II). Diurnal mean variances exceed the casual left right mean variances whether diurnal variances are calculated from pressures taken *on the same arm* or on the opposite arm. Diurnal variances are consistently although not significantly larger when calculated on the opposite rather than on the same arm. Diurnal left right variances are significantly larger than casual left right variances for both systolic and diastolic pressures. Diurnal and left right differences appear to be essentially additive but there is a suggestion that the magnitude of their effects may differ for systolic and diastolic pressures, and between males and females.

Comparison of the basal and casual intrapair variances *of monozygotic and of dizygotic* twins reveals marked differences in both systolic and diastolic pressure (Table III). In males the mean intrapair casual pressure variances are smaller than the basal pressure variances and this decrease

is statistically significant in monozygotic twins. In females, on the other hand the casual pressure variances are larger than the basal pressure variances, with the single exception of the diastolic intrapair variances in dizygotic twins

Whatever the influences are that differ between the basal and casual studies, they have an opposite effect upon the intrapair blood pressure variances in males and females. The casual intrapair variance is smaller than the basal intrapair variance in males and larger in females. This is also seen in the direct comparison of male and female intrapair variances. All female mean casual intrapair variances are larger than the male mean casual intrapair variances whereas all the female mean basal intra pair variances are smaller than the male mean basal intrapair variances, with the exception of the diastolic pressure variance in dizygotic twins.

The mean interpair and intrapair casual pressure variances of monozygotic and dizygotic twins (Table IV) differ from those calculated from basal pressures (Table II) All casual interpair variances are significantly larger than their corresponding intrapair variances this relationship was only found for monozygotic females in the basal studies. This difference between the two studies is a reflection of the consistently larger casual than basal interpair variances. In females the intra pair and interpair variances are increased proportionately with the result that the ratios of these variances are similar to those obtained in the basal studies. In males the casual interpair-intrapair variance ratios are considerably larger than their corresponding basal ratios because of the smaller intrapair and larger interpair variances.

The critical MZ DZ ratios give no indication of a genetic component of variability (as measured by this ratio) using casual blood pressure measurements. In the basal studies this ratio was at the .05 level of significance in females.

In females the correlation between systolic and diastolic pressure within the individual is slightly smaller when taken casually (Table V) than when taken basally (Table IV) In males the casual and basal individual correlations are similar whereas the casual cross-twin correlation is increased from r = .001 to r = .576. In males it would appear that in the presence of forces which affect casual blood pressure

Table III Intrapair mean variances of basal (left arm) and casual (right arm) measurements

		Males				Females			
			Variance	t	P		Variance	t	P
Systolic pressure									
MZ	Basal*	14	89 54	2 32	< 05	20	24 78	2 19	< 05
	Casual	14	27 00			20	45 60		
DZ	Basal	5	65 00	2 76	< 10	14	56 75	29	< 80
	Casual	5	15 60			14	65 00		
Diastolic pressure									
MZ	Basal	14	52 11	3 49	< 005	20	26 93	2 50	> 02
	Casual†	14	14 71			20	73 [illegible]		
DZ	Basal	5	17 20	08	< 80	14	57 71	1 22	< 20
	Casual	5	16 00			14	33 43		

*Male variance significantly larger than the female variance F = 3 61 P = .005 – .01
†Male variance significantly smaller than the female variance F = 4 99 P = [illegible] – .01

there is measurable genetic control of the relationship between systolic and diastolic pressure in the absence of these forces, i.e., in the basal study, genetic influence upon this relationship is not demonstrated. This is also reflected in differences between the correlations. In the basal studies the individual and MZ cross-twin correlations differ significantly (t = 2.50, P = .01 – .02); in the casual studies the difference is not significant (t = .565, P = .50 – .80). In females, genetic control of the relationship between systolic and diastolic pressure is apparent under the conditions of both the basal and the casual studies, i.e., the MZ cross-twin correlations differ significantly from zero in both instances. No significant differences are found between the MZ and DZ cross-twin correlations in either casual or basal studies.

Discussion

As far as was practicable to obtain, the basal blood pressure measurements are without transient environmental effects. Casual blood pressure measurements, on the other hand, are subject to the accumulative effects of environmental influences which in these data are the influences encountered by healthy young adults engaged in routine daily activites. In the data analyzed here, the effect of these environmental influences upon the measured level of the blood pressure is in accord with previous observations.[9,10] In both males and females the mean casual systolic pressure is significantly higher than the mean basal systolic pressure, whereas the mean diastolic pressure is not significantly affected. Comparisons of the monozygotic basal and casual intrapair pressure variances indicate, however, that the conditions of study not only have a differential effect on the systolic and diastolic pressures of males and females, but that there is also a sex difference in the manner by which genetic factors condition blood pressure variability.

The casual intrapair variances are significantly smaller than the basal intrapair variances for monozygotic males. In monozygotic females this is reversed, the casual intrapair variances are larger than the basal intrapair variances, and for diastolic pressure this increase is statistically significant. Because differences between basal and casual blood pressure measurements result from the transient effects of environmental stimuli, differences between the basal and casual intrapair pressure variances of

Table IV. Mean intrapair and mean interpair variances for monozygotic and dizygotic twins on casual blood pressure measurements (right arm)

	Males				*Females*			
		Variance	*F ratio*	*P*	*n*	*Variance*	*F ratio*	*P*
Systolic pressure								
MZ interpair	13	213.54			19	222.00		
			7.91	.001			4.87	.001
MZ intrapair	14	27.00			20	45.60		
			.58	.75			1.43	< .25
DZ intrapair	5	15.60			14	65.00		
			11.76	< .01			4.90	< .005
DZ interpair	4	183.50			13	318.46		
Diastolic pressure								
MZ interpair	13	194.92			19	181.06		
			13.25	.001			2.46	.025
MZ intrapair	14	14.71			20	73.53		
			1.09	.25			.45	< .75
DZ intrapair	5	16.00			14	33.43		
			10.72	> .01			3.42	> .01
DZ interpair	4	171.50			13	114.30		

monozygotic twins reflect the genetic control of blood pressure lability. The fact that these differences relate to sex differences in the genetic conditioning of a response to environmental stimuli and not to a lack of comparability in environmental influences, is seen from the uniformity of the increase in mean casual blood pressure and interpair variances in males and females. Basal blood pressure per se appears to be under stronger genetic control in females, whereas blood pressure lability is under stronger genetic control in males. It is also apparent from the cross-twin analysis that expression of genetic control in the relationship between systolic and diastolic pressure in males is dependent upon environmental stimuli.

The sex differences in the genetic control of blood pressure, and the apparent pattern of these differences observed here are of particular interest in view of the relationship of blood pressure lability to hypertensive disease[4,7,11,12] and the differences in the incidence and prognosis of primary and accelerated hypertension in males and females.[14]

Sex differences related to the genetic conditioning of blood pressure variability have been noted by other investigators. Hines[14] reported that male and female monozygotic twins differ in the similarity of their blood pressure in the same manner observed in the basal studies. Miall and Oldham[15] found significant and unexplained differences in the regression of the blood pressure of male relatives on that of female propositi. In the presence of sex differences reported here such an observation would be anticipated. In a study of industrial workers, D'Alonzo and associates suggest that mothers may contribute disproportionately to the positive family histories of hypertension. Pickering[9] noted a sex difference in the presence of high recorded blood pressure. Why such sex differences have not been recognized more frequently can be seen in part from the present data. The monozygotic intrapair blood pressure variances of males are greater than those of females in the basal studies. By contrast, in the casual studies the monozygotic intrapair variances of the male are smaller than those of the female. If the blood pressure measurements had been obtained under conditions intermediate between those maintained for the basal and casual studies, it may be presumed that this sex difference would not have been detected even with the relative precision of the twin method.

In deference to practical considerations, many investigators rely upon single casual blood pressure readings.[14] In all probability these are adequate for some purposes, although they would appear to be less effective than basal readings for detecting genetic variability in normal levels of blood pressure, and certainly single readings will not permit a study of blood pressure lability, which these data on twins indicate may be of considerable genetic interest. A number of investigators have studied the differences between basal

Table V. Correlations between measured casual systolic and diastolic pressures

Zygosity	Comparison			t†	P
MZ	Individual	14	715****	365	50–80
	Cross-twin	14	576		
MZ ♀	Individual	20	590*	416	50–80
	Cross-twin	20	489*		
				470	50–80
DZ ♀	Cross-twin	14	339	1 174	20–30
	Individual	14	693		

*P<.05 **P<.01 ***P .005 ****P .001
†t is calculated for the difference of the values of z.

and casual blood pressure measurements.[6-8] Smirk studied the relationship of basal blood pressure to the supplemental pressure in males and noted that the basal pressure in an individual did not indicate the probable level of the supplemental pressure He interpreted this as evidence of a second and independent variable in the supplemental pressure Although supplemental pressure cannot be analyzed directly with these twin data for the purpose of a sex comparison something relating to the secondary variable referred to by Smirk can be delineated by correlations of basal and casual intrapair differences When this is done it is found that the correlations for systolic pressure are r = −.514 P = .05 − .10 in males, and r = +.302 P = > .10 in females. The negative correlation in males would be expected on the basis of Smirk's observations. The difference between the male and female correlations is significant (t = 2.273 P = .02 − .05) indicating a further sex difference in some variable relating to the supplemental pressure.

The demonstrated effect which the conditions of study have upon the genetic interpretation of blood pressure measurements makes a consideration of the relative association of weight and ponderal index to basal and casual pressures of particular interest Kahler and Weber[1] reported that when *intrapair differences in blood* pressure were great in monozygotic twins it was the heavier member of the pair of twins who had the higher pressure. We did not find this simple relationship between weight and either basal or casual blood pressure measurements. Nor do the larger intrapair differences in weight consistently accompany the larger intrapair differences in blood pressure.

To examine statistically the possible relationship of weight to blood pressure the two members of every pair of monozygotic twins were separately classified as to the heavier same or lighter members and as to having the higher same or lower blood pressure. A similar tabulation was carried out with the ponderal index (stature/$\sqrt[3]{\text{weight}}$) No significant chi square values were found for the association of basal blood pressure with weight or ponderal index. The casual measurements gave different results the heavier twin and the twin with the smaller ponderal index more frequently had the higher systolic pressure. The chi-square values for casual systolic pressure with weight were significant in both males (P = .002) and females (P = .02) A smaller ponderal index also was significantly associated with higher casual systolic pressure in males (P = .01) but not in females. A further study of the association of these and other variables with blood pressure is presently in progress with more extensive data on twins.

Of interest here however is the demonstration of a relationship between weight and ponderal index and casual but not basal systolic pressure, and the relatively greater affect the conditions of study have upon these associations in males. The conditions of study and possibly differences between the sexes could account in part for some of the differences in the findings reported by various investigators.[14,21-23]

Summary

Basal and casual blood pressure measurements have been obtained under standardized conditions of study in 53 adult pairs of twins who were determined to be in good general health on the basis of health histories and medical examinations These *data have afforded an analysis of differences* between the left and right arms and differences between casual and basal blood pressure measurements in individuals, and within and between pairs of twins.

In both the casual and basal studies it can be seen from the critical MZ DZ ratios that variability in the measured levels of the blood pressure (in these adult subjects in good general health) is predominantly under environmental influences. However different comparisons of the monozygotic twin intrapair casual and basal variances indicate that there may be genetic as well as sex influences which are not effectively defined by single blood pressure measurements, at least in the normal range of this variable

It was found that (1) Although the average of the blood pressures is unaffected by the arm employed differences between

pressures on the left arm and those on the right arm are an important consideration when comparing measurements taken on the same individual or between the two members of a pair of twins. (This would also be an important consideration in the study of siblings and families.) (2) The conditions of study have a greater effect upon the interpretation of blood pressure data than might be implied by the relatively small differences in the average of the blood pressures taken under varying conditions of study (3) Measurement of genetic, environmental and sex influences upon blood pressure as well as the association of blood pressure with such variables as weight and ponderal index depend upon the conditions of study (4) There are genetic and sex-influenced factors related to cardiac function which are not effectively described by single measurements of the level of the blood pressure.

The analyses of these data on twins pose the question whether measured levels of the blood pressure constitute the most critical manifestation of the genetic and sex influenced variables to be investigated The lability of the blood pressure its reactivity to specific stimuli the relationship of systolic to diastolic pressure and, possibly the correlation of blood pressure with other attributes may be the most promising avenues for further genetic investigations of this clinically important measurement.

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Anomalous pulmonary venous drainage in relation to left superior vena cava and coronary sinus

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In a previous publication,[1] the figure-of-eight configuration in the chest film was described as an easily recognizable sign of total anomalous pulmonary venous drainage (a sign which, however, may be less evident in infants and very young children). In these cases all of the pulmonary venous blood flows into a wide venous arch formed by a left vertical vein (tentatively called *left vena cava*), the left innominate vein, and the right superior vena cava. This arch is responsible for the upper half of the figure-of-eight pattern, of which the heart itself constitutes the lower half. The blood is conducted from the right side of the heart to the left by way of an atrial septal defect (or patent foramen ovale). Nevertheless, the pulmonary circulation usually exceeds the systemic circulation by far, and there may be pulmonary hypertension. The left heart is underdeveloped in many of the cases.

Doubt was expressed, however, whether the left vertical vein† into which all pulmonary veins drain really should be considered a left superior vena cava, because it was thought to be necessary for embryological reasons that the term should be reserved for a vessel joining the left subclavian and innominate veins to the coronary sinus (Fig. 1). To understand this one must bear in mind the fact that the left superior vena cava is equivalent to the persisting left anterior cardinal vein, which in an early stage continues into the left sinus horn ("left duct of Cuvier") and that normally this left anterior cardinal vein and the cranial part of the left sinus horn are reduced in an early stage of development and finally obliterated,‡ thereby forming Marshall's ligament, whereas the caudal part of the left sinus horn (i.e., the part entering the heart) is transformed into the coronary sinus (Fig. 2).

In our earlier cases of total pulmonary venous drainage into the left vertical vein we found no connection with the coronary sinus.§ Since then we have been able to verify at operation or autopsy 25 cases of complete or partial abnormal drainage into the left vertical vein and (or) the coronary sinus. Among them are cases of drainage into the left vertical vein, when this vein is connected to the coronary sinus by a narrow communication, and many more cases in which a ligament joining the coronary sinus to the vertical vein was

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†In a recent editorial, Elliot and Edwards[2] used the term *anomalous vertical vein*.

‡A case of left anterior cardinal vein persisting into a later embryonic period than normal was described by Dankmeijer.

§Neither was this connection found by Neill, who even doubted its occurrence.



Fig. 1 Schematic drawing of complete left superior vena cava.

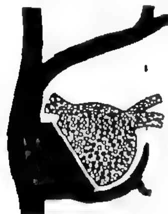


Fig. 2 Left superior vena cava obliterated as usual.

found at autopsy or seen by the surgeon (Professor A. G. Brom) at operation. Moreover, in some cases of drainage into the coronary sinus, a left superior vena cava was seen to enter the coronary sinus as well, occasionally receiving also pulmonary veins itself.

We feel confident, therefore, that the left vein may rightly be called *left superior vena cava*; this term will be used from now on.

The pulmonary venous return into the left superior vena cava and coronary sinus was distributed in a variable manner. In 11 cases all pulmonary venous blood flowed via the left superior vena cava into the left innominate vein or, rather, a short venous trunk leading to it; in 5 cases all pulmonary venous blood drained into the coronary sinus, whereas in 6 cases the pulmonary venous return, although totally abnormal, drained into several venous channels simultaneously, namely, the left superior vena cava, the coronary sinus, the right superior vena cava, and the inferior vena cava in various combinations (see Table I and Figs. 3 and 10). Finally, in 3 cases, part of the pulmonary venous blood entered the left atrium in a normal way, whereas the remainder drained into the superior left vena cava. In addition to our earlier statement that in the vast majority of cases a connection between the left superior vena cava and the coronary sinus (either a ligament or a functioning vein) was found, we want to point out that in Case 24 the venous connection was of the same size as the superior vena cava itself and that, moreover, the pulmonary venous flow appeared to have been directed toward both ends (i.e., left innominate vein and coronary sinus). In Case 25 the left superior vena cava appeared to be complete but entered a monoatrium; the sinu-atrial wall and interatrial septum were absent.

In the context of this article there is no room for a comprehensive review of all possibilities of abnormal pulmonary venous return. We are only concerned with the cases which show a partial or complete drainage into the system of the left superior vena cava and the coronary sinus. In the case of partial drainage into this system the other pulmonary veins entered the left atrium, the right superior vena cava, or the inferior vena cava.

We collected 25 verified cases (18 examined anatomically, and the other 7 verified only by the surgeon during operation). The data are given in Table I and are discussed below.

There was still another autopsy case (that of J. M., 6 days old) which was not included in the Table although it deserves to be recorded briefly here. The rather complicated findings consisted of: (a) drainage of the right pulmonary veins into the portal venous system via the left gastric vein, (b) a network of irregularly

*We wish to thank Dr Gonsalbeeren and Dr Hermans (Breda) for sending us two specimens, Dr Bockmuhl (Delft) for sending another, and also Dr Schwidetsk (Aruba) for sending two specimens.

dilated and tortuous pulmonary veins from the left lung which drained into both a small sized left superior vena cava and by way of a vascular ring into the thymic venous system. In addition there was absence of the coronary sinus, pulmonary atresia with patent ductus arteriosus and a minimal collateral bronchial circulation. Two atrial septal defects were present in the position of the foramen ovale and the (absent) coronary sinus respectively. The number of noncardiac anomalies included splenic aplasia, displacement of the biliary vesicle, absence of the umbilical artery, and a division of the left lung into four lobes.

Although this case showed a left superior vena cava with abnormal pulmonary venous drainage, it was thought to be essentially different from the other cases on account of its irregular and complicated nature and its presumably different mode of origin in the course of embryonic development. We imagine that it represents in part at least the persistence of primitive more or less haphazard connections between the pulmonary and splanchnic venous systems instead of the regular pattern formed by the entrance of pulmonary veins into (or perhaps as an outgrowth from) the caval system.* For these reasons this case was not listed in the table. The anatomic findings are shown in Fig. 4.

It is also interesting to note in this case the occurrence of drainage of pulmonary venous blood into both the portal and the left superior caval systems. In this respect, too, the specimen is unique in our collection.

All the other cases listed in the Table can readily be divided into a few categories consisting of complete or partial pulmonary venous drainage into the persisting upper and (or) lower end of a left superior vena cava.

It should be noted that in all cases an atrial septal defect in the position of the foramen ovale, but varying in size, was present.† There were additional anomalies in 9 of the cases, namely, ventricular septal defects in Cases 5, 16, 21, 24, and 25, aortic atresia with congenital mitral stenosis in Case 14, pulmonary atresia in Cases 11 and 25, aortic transposition in Cases 8, 11, 13, and 25, common atrioventricular canal in Cases 8, 11, and 20, and connection of the inferior vena cava to the left atrium and of the hepatic veins to the right atrium in Case 8.*

Group A contains 14 cases of total or partial pulmonary venous drainage into the (upper) left vena cava, with the flow of blood being directed toward the left innominate vein. Most of these cases (8) showed total abnormal drainage without a patent communication—as distinct from a ligament—with the coronary sinus.

Three cases of total abnormal drainage which did show a small communication with the coronary sinus without any evidence of pulmonary venous blood flowing into it have been designated as Subgroup A_{II}. Subgroup A_{III} comprises 3 cases of partial pulmonary venous drainage into the left superior vena cava. No venous or even ligamentous connection with the coronary sinus was found.

Group B, on the other hand, contains 7 cases of total or partial pulmonary venous drainage into the lower end of the left superior vena cava, i.e., into the coronary sinus. In 5 of these cases, taken together in Subgroups B_I and B_{III}, respectively, a left superior vena cava in the usual sense was absent.

In the other 2 cases (19 and 21, B_{II} and B_{IV}) the upper half of the left caval vein was fairly small and did not appear to carry pulmonary venous blood (confirmed in Case 19 by catheterization of the heart). There was total anomalous drainage in all cases of this group, but in Cases 20 and 21 the right upper pulmonary veins entered the right superior caval vein. Moreover, in Case 21 the right lower pulmonary veins drained into the inferior vena cava.

Finally, Group C represents combined drainage in both a caudal direction (into the coronary sinus) and a cranial direction (into the left innominate vein). In 2 of the 4 cases in this group the upper and lower part of the vena cava formed separate sites of drainage (Subgroup C_I). In the other 2 cases the left superior vena

*For [illegible] discussion of the connections between splanchnic and cardinal venous systems and the outgrowth of pulmonary veins from the primitive [illegible] we refer to Dankmeijer and Los.

†This was, therefore, not mentioned in the individual cases of the Table. However, multiple atrial septal defects are listed.

*In Cases 8 and 25 there was also situs inversus of the heart and lungs and splenic aplasia.

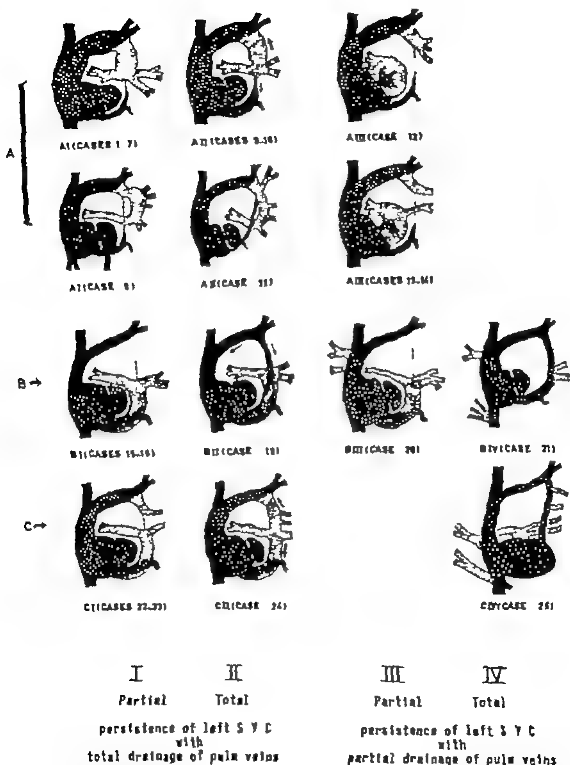


Fig. 3. Diagrammatic survey of different combinations of complete or partial persistence of left superior vena cava with complete or partial anomalous pulmonary venous drainage. *A*, Total or partial drainage into upper end of left superior vena cava. *B*, Total or partial drainage into lower end of left superior vena cava. *C*, Drainage into both ends of left superior vena cava.

Table I Details of cases

Group A Drainage of pulmonary veins into left superior vena cava (upper part of left cardinal system)
Subgroup A₁—*All pulmonary veins draining into left superior vena cava. No communication with coronary*

1 J C E H male 11 months old—A 745
Progressive cyanosis and dyspnea X-ray figure-of-eight RA pressure 100/8 mm Hg, no pulmonary stenosis Ligament between left SVC and CS. No additional anomalies

2 M A male 9 months old—A 1400
Slight cyanosis and dyspnea. Heart failure X-ray figure-of-eight. No heart catheterization. Ligament between left SVC and CS. No additional anomalies

3 L B male 1 ½ years old—A 1458
Cyanosis and dyspnea. Repeated respiratory infections X-ray: figure-of-eight. RA pressure 110 10 mm. Hg no pulmonary stenosis. Died during initial stage of operation. Ligament between left SVC and CS Two atrial septal defect

4 C D male 3 years old—A2412
Cyanosis and dyspnea. Repeated respiratory infections. X-ray figure-of-eight. No heart catheterization. Died after surgical correction No ligament between left SVC and CS. No additional anomalies

5 P W R H P male 3 months old—A 2708
Progressive cyanosis and dyspnea. X-ray slightly suggestive of figure-of-eight. PA pressure 60-30 mm Hg Death after banding of main pulmonary artery and ligation of small patent ductus Additional anomaly small apical VSD Ligament between left SVC and CS

6 A M male born Dec 27 1953—C 541/55
Slight cyanosis X-ray figure-of-eight. PA pressure 36/19 mm Hg Operation in 1958 for correction of pulmonary venous drainage small ASD left for safety Recatheterization in 1961 RA pressure 25/0 mm Hg very small ASD No ligament between left SVC and CS

7 J H L male born June 15 1930—C 7263/54
Cyanosis and dyspnea. X-ray figure-of-eight RA pressure 55/0 mm. Hg PA pressure 55/10 mm Hg Successful surgical correction in 1960 Ligament between left SVC and CS. A B lished Case 3 by Snellen and Albers. The existence of the previously found infundibular pulmonary stenosis was not confirmed

8 T C male 3 months old—A 3063
Slight cyanosis and dyspnea. X-ray figure-of-eight dextrocardia. No heart catheterization Additional anomalies situs inversus transposition of the aorta, common AV canal infundibular pulmonary stenosis, partial absence of atrial wall. Hepatic veins drained into RA IVC into LA. Patent ductus Splenic plasia. Ligament between upper part left SVC and CS

Subgroup A—*All pulmonary veins draining into left superior vena cava Small communication with coronary*

9 R.T S male 5 months old—A 1065
Cyanosis and dyspnea Heart failure X-ray suggestive of figure-of-eight No heart catheterization Died 1 day after surgical correction

10 J J female born May 27 1951—C 886/55
Cyanosis and dyspnea X-ray figure-of-eight. PA pressure 60/24 mm. Hg First operation in 1956 correction of pulmonary venous drainage Recatheterization 1959 PA pressure 40/10-20 mm Hg ASD with predominant L R shunt. Second operation in 1959 closure of ASD

11 H P M C female, 10 months old—A 3044
Cyanosis and dyspnea Repeated respiratory infections. Heart failure X-ray right SVC dilated No heart catheterization. Clinical diagnosis arterial transposition with pulmonary stenosis Autopsy findings total drainage into left SVC transposition with pulmonary atresia common AV canal Small communication between upper part of left SVC and CS. Below this communication the common pulmonary venous trunk passed between superior branch of left PA and bronchus

Subgroup A₁₁—*Some pulmonary veins draining into left superior vena cava No communication with coronary*

12. M J C B female born May 9 1931—C 7270/56
No cyanosis slight dyspnea X-ray no figure-of-eight but suggestion of left SVC. Normal pressures Successful operation 1958 No ligament between persistent part of left SVC and CS

*Verified at operation
**Verified at autopsy
SVC Superior vena cava CS Coronary sinus PA Pulmonary artery (or arterial). ASD Atrial septal defect. RV Right ventricular AV Atrioventricular IVC Inferior vena cava. LA Left atrium. L-R Left to right. RA Right atrium
VSD Ventricular septal defect. MI Mitral insufficiency TI Tricuspid insufficiency
Table I is continued on pages 189 and 190

Table I Details of cases—Cont'd

Subgroup A III—*Some pulmonary veins draining into left superior vena cava. No communication with coronary sinus*—Cont'd

13 ** M. A., male, 2 months old—A 2588
X-ray: no figure-of-eight. Anatomic findings: left upper pulmonary vein into left SVC, arterial transposition. No ligament

14 M. V., female, 5 days old—A 11
Died from aortic atresia with mitral stenosis and rudimentary left ventricle. Left upper pulmonary vein into left SVC. No ligament

Subgroup A IV—*Some pulmonary veins draining into left superior vena cava. Communication with coronary sinus*
This would require either normal connection of one or more pulmonary veins or anomalous drainage elsewhere (e.g., right SVC). No such cases are present in our material

Group B Drainage of pulmonary veins into coronary sinus (lower part of left caval system)

Subgroup B I—*All pulmonary veins draining into coronary sinus. No left superior vena cava*

15 L.L., male, 1 year old—A 88
Slight cyanosis and dyspnea. Respiratory infections. X-ray: bulging of RA, and left cardiac contour. No heart catheterization. No additional anomalies

16. J. P.S., 3½ years old—A 372
Cyanosis and dyspnea. Repeated respiratory infections. X-ray: bulging of RA and left cardiac contour. No heart catheterization. Two small apical VSD, annular aortic stenosis

17 ** M. Z., male, 5 weeks old—A 2942
Cyanosis and severe dyspnea. X-ray: bulging of RA and left cardiac contour. RV pressure 60/0 mm. Hg. Death after operation. No additional anomaly

18 F.A.W., male—C 995/49-50
Slight cyanosis, dyspnea. Frequent respiratory infections. X-ray: bulging of RA and left cardiac contour. I. 1953: RV pressure 75/5 mm. Hg. PA pressure 60/10 mm. Hg. I. 1956: RV pressure 108/15 mm. Hg. PA not reached. Operation in 1959 was successful

Subgroup B II—*All pulmonary veins draining into coronary sinus. Small left superior vena cava*

19 G.V., male, born Oct. 30, 1952—C 508/59
Slight cyanosis and dyspnea. X-ray: slight bulging of RA and marked left cardiac contour. PA pressure 42/10 mm. Hg. Operation in 1960 was successful

Subgroup B III—*Some pulmonary veins draining into coronary sinus. No left superior vena cava*

20 ** C.M., female, 4 years old—A 2564
Cyanosis and severe dyspnea. PA pressure 45/15 mm. Hg. Clinical diagnosis: ventral (primum type) ASD with MI and TI. At operation, anomalous drainage also found. Death from AV block. Left and lower right pulmonary veins into CS, upper right pulmonary vein into right SVC

Subgroup B IV—*Some pulmonary veins draining into coronary sinus. Left superior vena cava present, communication with coronary sinus*

21 ** J. B., female, 4½ weeks old—A 2941
Slight cyanosis, severe dyspnea. Heart failure. X-ray: marked bulging of left cardiac contour, slight bulging of RA. Death after emergency operation. Anatomic findings: upper right pulmonary veins into right SVC, lower ones into IVC, left pulmonary veins into CS, high VSD. Persistent left SVC

Group C Drainage of pulmonary veins into both left superior vena cava and coronary sinus

Subgroup C I—*Some pulmonary veins draining into left superior vena cava, the remainder into coronary sinus. No communication between left superior vena cava and coronary sinus*

22 G.A.W.K., female, born Aug. 29, 1957—C1212/59
Slight cyanosis and dyspnea. X-ray: marked bulging of RA, less so of left cardiac contour. RV pressure 65/8 mm. Hg. Operation in 1959: successful. Ligament between left SVC and CS

23 ** R.J., male, 1 year old—A 2976
Cyanosis and dyspnea. X-ray: bulging of RA and of left cardiac contour. RV pressure 65/0 mm. Hg. Death after operation. No additional anomalies. No ligament

Subgroup C II—*Some pulmonary veins draining into left superior vena cava, the remainder into coronary sinus. Communication between left superior vena cava and coronary sinus*

24 ** P.B., male, 8 months old—A 2702
Cyanosis and dyspnea. X-ray: bulging of RA and of left cardiac contour, suggestion of left SVC. No heart catheterization. Sudden death. Anatomic findings: left pulmonary veins into left SVC and CS, right pulmonary veins into CS. Wide communication between left SVC and CS. Additional anomaly: small VSD

For footnotes see page 188. Table is concluded on page 190.

Table I Details of cases—Cont d

Group C Drainage of pulmonary veins into both left superior vena cava and coronary sinus—Cont d

Subgroup C_{III}—*Some pulmonary veins draining into both ends of left superior vena cava. No communication between left superior vena cava and coronary sinus.*

This would mean one or more other pulmonary veins either normally connected to the left atrium or anomalously to some other venous structure (e.g., right SVC) or the to right atrium. No such cases were found in our material.

Subgroup C_{IV}—*Some pulmonary veins draining into both ends of left superior vena cava. Wide communication between left superior vena cava and monoatrium*

25 M. K., female, 4 months old—A 2743
Progressive cyanosis and dyspnea. X-ray: heart displaced to the left with marked bulging of left cardiac contour. No heart catheterization. Anatomic findings: left lung draining into left SVC and monoatrium right lung draining into right SVC and IVC. Absence of sinuatrial wall, juxtaposition of auricles, monoatrium, pulmonary atresia, rudimentary right ventricle with small VSD, one single AV orifice. Splenic and left renal aplasia.

cava constituted a complete venous connection between the left innominate vein and either the coronary sinus or a monoatrium. In Case 24, constituting Subgroup C_{II}, anomalous pulmonary venous drainage into the left caval system was complete; in Case 25 (Subgroup C_{IV}) the pulmonary veins from the right side entered the right superior vena cava and inferior vena cava.

The anatomic dissection of our autopsy specimens was preceded by selective filling with barium sulfate and roentgenologic examination as described in a previous article. Fig. 5 shows the result obtained in a case of drainage into the coronary sinus and Fig. 6 illustrates the total drainage into a left superior vena cava.

In so far as clinical details are concerned some data are tabulated which might be of interest. These concern the age of our patients, the absence or presence of pulmonary hypertension (if catheterization of the heart could be performed), the clinical history, and the reliability of preoperative diagnosis with particular reference to the diagnostic value of the chest film.

The age at death of our 10 patients who came to autopsy without undergoing an attempt at surgical correction of their condition (Cases 1, 2, 8, 11, 13, 16, 24, and 25) varied from 5 days to 3½ years. In this group, 6 patients showed additional anomalies. In one of them, Case 16, two small interventricular septal defects and annular aortic stenosis were present, all presumably without much clinical importance. However, in the other 5 (Cases 8, 11, 13, 14, and 25), who were from 5 days to 10 months of age, the main cardiac defects which appeared to be the cause of death were aortic atresia in Case 14, pulmonary atresia in Cases 11 and 25, common atrioventricular canal in Cases 8 and 11, and aortic transposition in Cases 8, 11, and 13. Moreover, whereas all other autopsy cases (both with and without previous operation) displayed *total* abnormal venous return, the abnormal drainage in 2 (Cases 13 and 14) was only partial (from the left upper lobe in both cases). It is obvious that this anomaly per se could hardly have been responsible for the fatal outcome.

In 8 patients (Cases 3, 4, 5, 9, 17, 20, 21, and 23) surgical intervention was followed by death within 10 days. Here the age varied from 4½ weeks to 4 years. It should be noted that in the oldest patient (Case 20, a 4-year-old girl) a common atrioventricular canal was present; in Case 5 there was a ventricular septal defect and a small but patent ductus arteriosus; in Case 21 again a (small) ventricular septal defect; and in Case 3 two atrial septal defects and severe pulmonary hypertension. It is likely that in some of these cases the surgical result was also influenced by a partially or wholly incorrect diagnosis.

Lastly, 7 patients (Cases 6, 7, 10, 12, 18, 19, and 22) underwent cardiac surgery with a good result. The age at operation varied from 2 years to 30 years, with a mean of 12½ years. Postoperative follow-up of these patients for a period of 2 to 6 years proved them to be in excellent condition except for the onset of atrial flutter one-half year after operation in Case 22.

(This has since been corrected.) The atrial septal defect was closed in the first instance, i.e., at the time of correction of the anomalous return in 5 cases. In Case 10 the defect was closed during a second operation 3 years later, and in Case 6 the defect proved to be of little importance at recatheterization 3 years after operation. It was thought that a further operation was not necessary. There were no additional anomalies in this group.

Pulmonary arterial pressure was recorded during catheterization of the heart in 8 patients; the systolic pressure was found to be 60 mm. Hg in 3 patients (Cases 5, 10, and 18). Right ventricular systolic pressure was found to be higher than 60 mm. Hg in an additional group of 5 patients (Cases 1, 3, 17, 22, and 23) in whom pulmonary arterial pressure could not be recorded, but in whom pulmonary stenosis was excluded at operation or autopsy.

Heart failure, or at least severe dyspnea often associated with recurrent bronchitis, was present in 11 patients (Cases 1, 5, 9, 11, 16, 17, 21, 25). Mild cyanosis and dyspnea were common signs in all other patients.

The diagnosis of abnormal pulmonary venous return was made in half of the cases before autopsy or operation. In at least 4 other patients (Cases 1, 5, 9, 24), all under 1 year of age, the diagnosis could have been made on the basis of a not very conspicuous but still recognizable figure-of-eight pattern on the chest film. In Cases 1, 5, and 9 there was complete drainage into the left superior vena cava. In Case 24 pulmonary venous return was directed in part toward the coronary sinus, thus lessening the flow through the left superior caval vein.

In Case 23 the abnormal venous return into the left superior vena cava was diagnosed, but coexisting partial drainage into the coronary sinus was overlooked. Diagnostic difficulties were also encountered in Case 17, because venous angiocardiography from the femoral vein filled mainly the left heart through the atrial septal defect, thus suggesting tricuspid obstruction, and in Case 20 because the clinical picture was dominated by the existence of a common atrioventricular canal. In several cases a complete clinical examination was not possible because of the very young age and critical condition of the patient, or because of other circumstances.

From a review of the chest films of our cases of abnormal drainage into the coronary sinus, it seems evident that the configuration of the cardiac shadow is less characteristic than in cases of total or even subtotal drainage into the left superior vena cava. However, as stated in a previous publication[4] and confirmed by Keith and associates,[4] a bulging of the right atrial contour high above the diaphragm and generalized bulging of the left cardiac contour (sometimes with particular prominence of the pulmonary arc) appear to be suggestive diagnostic signs in the chest film (Fig. 7). As a rule, the roentgenologic pattern is more characteristic in older children and adults than in infants. This applies also or even more so to the figure-of-eight pattern, as has been stated repeatedly in the literature. The diagnosis of a persisting left superior vena cava without pulmonary venous drainage is often possible on the routine chest film, particularly when the shadow of a persisting thymus, so often leading to confusion in infants, is absent. Planigrams may be useful, especially in partial pulmonary venous drainage (in the present series, which is concerned with persistence of the

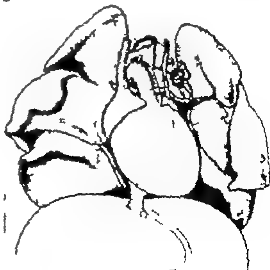


Fig. 4. Patient J. M., 6 days old. For description, see text.

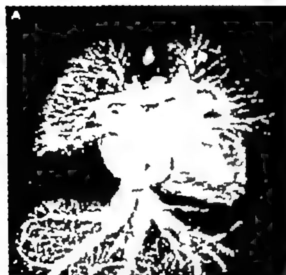




Fig. 5. A, Postmortem filling with barium of heart (Case 15) with total anomalous pulmonary venous drainage into the coronary sinus. B, Schematic drawing of A.

left superior vena cava (from the left lung or its upper lobe) and subsequent slight dilatation of the left caval vein. Venous angiocardiography by injection of contrast substance into the left cubital vein may give still more conclusive information. In Fig. 8 we see the contrast flowing into the left superior vena cava, from whence it is washed out again by the upward flow of pulmonary venous blood. For a discussion of the angiocardiographic diagnosis of pulmonary venous drainage into the coronary sinus we refer to Rowe, Glass, and Keith.[8] Fig. 5 shows the postmortem roentgenologic aspect of our Case 15.

In order to clarify the relationship of the left superior vena cava to the coronary sinus and the pulmonary veins draining into them, and also to obtain a comprehensive visual review of our cases, a series of schematic drawings was made. These were grouped according to the anatomic situation of the left superior vena cava and the drainage of the pulmonary veins.

The normal pulmonary venous arrangement with or without persistence of the left superior vena cava is illustrated in Figs. 1 and 2.

In the comprehensive collection of diagrams (Fig. 3) the three main patterns of pulmonary venous drainage in relation to persistence of the left caval system are represented as follows: in the upper double row (*A*) part or all of the pulmonary veins are connected with the upper part of the left caval vein; in the middle row (*B*) the connection is with the lower part (coronary sinus); and in the lower row (*C*) the pulmonary veins are connected to both the upper and the lower part of the left superior caval vein. The letters *A*, *B*, and *C* indicate the same groups as in Table I.

On the other hand, the vertical rows contain the following patterns of arrangement of pulmonary veins in relation to persistence of the left caval system: *I*, partial persistence of left caval system connected to all pulmonary veins; *II*, total persistence of the left vena cava, again connected with all pulmonary veins; *III*, partial persistence of the left vena cava

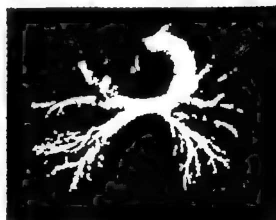


Fig. 6. Total pulmonary venous drainage into left superior vena cava (Case 2). The veins which constitute the upper half of the figure-of-eight have been tied off in the middle in order to avoid obscuring the pulmonary veins from the right lung. However, a faint filling of the right superior vena cava is seen.



Fig. 7. Chest film of Case 18. Total anomalous pulmonary venous drainage I to coronary sinus.

with part of the pulmonary veins entering into it and IV total persistence of left caval vein with drainage of part of pulmonary veins. As stated earlier the diagrams representing Subgroups B_{III} and B_{IV} (Cases 20 and 21) as well as Subgroup C_I (Case 25) show a partial anomalous drainage only in respect to the left caval vein the other pulmonary veins are also abnormally connected however.

The comparison of this diagrammatic survey with the data of the table is facilitated by [illegible] arrangement, in that the designation *A*, *B* and *C* for the horizontal rows and *I*, *II*, *III* and *IV* for the vertical columns are used in the same way as in the Table. For example therefore the Subgroups A_I and B_{II} are to be found at the intersection of horizontal row *A* and vertical row *I* and of horizontal row *B* and vertical row *II* respectively. The case numbers of each specific diagram are also shown in the figure. As in the Table the term *connection* is used only for a functioning communication.

As will be seen from the diagrams Cases 8 and 11 showed a pattern which was slightly different from that of the other cases in Subgroups A_I and A_{II}. In Case 11 a connection of the left superior vena cava with the coronary sinus was found originating higher than usual however that is above the entrance of the right and lower left pulmonary veins (Fig. 9). In exactly the same position in Case 8 there was a ligament instead of a venous connection. It is not yet clear to us whether the vessel formed by the junction of the right and lower left veins and tentatively called *pulmonary venous trunk* indicates any specific peculiarity in embryonic development. It may however be of some interest to the surgeon to know the possibility of this variation.

Because the variability in Group A appeared to be somewhat greater than that in the other groups two diagrams in vertical rows *I* and *II* were used to show these variations. Also it is to be noted that simultaneous drainage into the left and

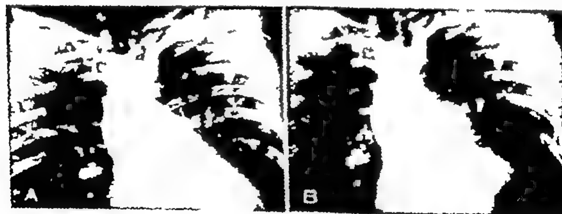


Fig. 8. A, Venous drainage from the left lung into the upper part of the left superior vena cava (Case 12). Angiocardiogram from left cubital vein. Injected contrast starts to [illegible] both the left and right superior venae cavae. B, 1 to 2 seconds later the contrast is washed out again from the left superior vena cava.



Fig. 9. Venous arc formed by the left superior vena cava (upper end) and the anomalous vessel draining the right and the lower left pulmonary veins. Small communication with the coronary sinus. Note also the pulmonary venous trunk passing behind the upper branch of the left pulmonary artery. (Case 11.)

right venae cavae occurred only in a minority of the cases.

The Subgroups A_I and C_{III} are not represented in our collection but should be considered as possible variations. On the other hand, cases such as that illustrated in Fig. 4, which do not fit into the scheme because of a highly irregular pattern, are probably very rare.

It must be stipulated that the dotted lines joining the persisting parts of the left superior caval vein are no more than a schematic indication of our concept. However, inasmuch as this concept, which holds that the left vertical vein described in our original report on the figure-of-8 configuration[1] is identical with the main (upper) part of the left superior vena cava, appears to be fully justified on the strength of the evidence, the dotted lines are also permissible. Moreover, they represent in their caudal part the ligament which is often found at operation or at autopsy, as mentioned earlier. The distance covered by this ligament does not reach higher than the upper pericardial border in normal circumstances, or in cases of Group B_I in which the ligament was also occasionally found. In cases of Group A_I the ligament was quite often seen to connect the coronary sinus to the upper part of the left superior vena cava, thereby completing the whole original system.

Discussion

The main point of our article concerning the relationship of the left superior vena cava to an anomalous pulmonary venous drainage does not require further comment. It is obvious that within the group of cases showing the coexistence of abnormally connected pulmonary veins and a partially or totally persisting left superior vena cava, drainage into the cranial part of the left superior vena cava occurs most frequently. Moreover, within the whole of our clinically examined and verified material of total anomalous pulmonary venous drainage (including different sites of drainage such as the direct connection of all pulmonary veins to the right atrium) the figure-of-8 pattern constitutes the largest group (17 in a total of 31 cases[4]). Finally, we have not encountered any case in which abnormally connected pulmonary veins did not use, at least in part, the pathway of the left superior vena cava, if such a vessel was present at all.

The relative frequency of the various patterns illustrated in Fig. 3 and described in Table I is shown in Fig. 10.

With regard to the clinical aspects which were mentioned briefly, we can state that it is not superfluous to stress once more the relative frequency of these cases and the rich variety of anatomic and functional arrangements, which, however, is relatively easy to understand if one bears in mind the embryonic development. In our material a correct diagnosis was made in only half of the cases. As stated earlier, in many cases either an additional and much more serious cardiac defect tended to mask the diagnosis or an extensive clinical examination was not possible because of the very young age and critical condition of the patient. In other cases, however, incorrect interpretation of the chest film, of the angiocardiogram (as in Case 17 mentioned earlier), or of catheterization data was responsible for missing the exact or at least the complete diagnosis. The simplest way to avoid these errors is

to be constantly aware of the fairly common occurrence of the various anatomic and functional patterns depicted in the diagrams. To these should be added of course still other varieties (e.g. complete or partial drainage into the right atrium, the right superior or inferior vena cava, and the portal venous system) which have been left out or were merely mentioned briefly because they did not concern us here, except in so far as they were combined with drainage into the left superior caval system.

In 8 of the 13 cases in which the pulmonary arterial or right ventricular pressure could be ascertained, the existence of a significant pulmonary hypertension (i.e. systolic pressure of 60 mm. Hg and higher) was established. Pulmonary pressure was known in but 1 of the 10 patients who came to autopsy without previous operation; this patient (Case 1) had pulmonary hypertension. Among the patients who died within 10 days after operation (8 cases), pulmonary pressure was known in 5 and was found to be elevated in 4 of them. In the other patient (Case 20) common atrioventricular canal was present. Two patients (Cases 10 and 22) who were known to have pulmonary hypertension (moderate, however, i.e., with systolic pressures of 60 and 65 mm. Hg) are doing well after operation.

The surgical risk was definitely correlated to the age of the patient, as was pointed out recently by Brums, who had a somewhat larger material than that described in Table I. Of a total of 18 patients, 8 survived the operation for total anomalous pulmonary venous connection, but among those under 4 years of age only 1 survived out of 10, whereas among those who were 4 years or older 7 survived out of 8. It should be noted that, apart from a generally greater risk in infants, a more or less alarming clinical condition was present in the younger age group before operation, and this, in fact, was responsible for the decision to operate at an early age.

No occlusion or narrowing of pulmonary veins was encountered in the anatomic specimens of this series; neither was there in any of our cases an indication of inadequate dilatation of the efferent great veins, such as left and right superior venae cavae or coronary sinus. On the contrary, the degree of dilatation appeared always to depend largely on the age of the patient, that is, on the length of time during which the increased flow had been in existence and on the magnitude of pulmonary venous return through these vessels, as deter

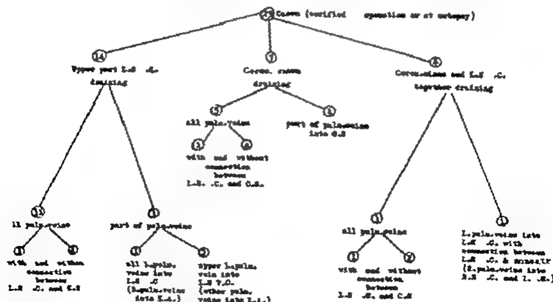


Fig. 10 Frequency of various patterns in 25 cases of abnormal pulmonary venous connection with left superior vena cava and (or) coronary sinus.

mined by the number of pulmonary veins and the lung volume involved. The left superior vena cava was always found in front of the pulmonary artery. However, in Case 11 (Group A_{II}), in which the course of the (small) lower left superior caval vein was somewhat unusual, the common pulmonary venous trunk passed between the upper branch of the left pulmonary artery and the left bronchus (Fig. 9). Here a narrowing as discussed by Elliott and Edwards[2] for the so-called anomalous vertical vein can be assumed.

A systematic microscopic examination of small pulmonary arteries and arterioles was not carried out in the present study. However, microscopic findings in these vessels were available in 8 cases and revealed moderate to marked medial hypertrophy in half of them, with slight or no changes in the others. This conclusion is not very different from that of Sherman and Bauersfeld, who stated that "the muscular arteries and arterioles generally have hypertrophied smooth muscle coats" and added that there was "absence of degenerative changes and intimal scars in these vessels."

Summary

Twenty-six cases are described of total or partial anomalous pulmonary venous return into a persisting left superior vena cava or into the persisting components thereof, namely, the left "vertical vein," which forms part of the venous arc in the figure-of-eight pattern, and the coronary sinus. In many instances of incomplete persistence a ligament was found between the left vena cava and coronary sinus instead of a venous connection. Various patterns of the relationship of the completely or incompletely persistent left superior vena cava to anomalous pulmonary venous return were encountered, showing gradual transition from one to the other. Some clinical details are added, particularly in regard to the radiologic diagnosis.

The assistance of Miss H. C. [illegible] Ingen is gratefully acknowledged.

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Loss of reactivity of the pulmonary vascular bed in primary pulmonary hypertension

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Pulmonary vasoconstriction has been proposed as the most probable mechanism for the pulmonary hypertension in patients with primary pulmonary hypertension. Potential vasodilator agents such as Priscoline, hexamethonium, and reserpine have had little effect in decreasing the pulmonary arterial pressure in these patients. On the other hand, the intracardiac infusion of acetylcholine has produced significant decrements in the level of pulmonary hypertension. The purpose of this discussion is to present follow-up data in a subject with primary pulmonary hypertension in whom the reactivity of the pulmonary vascular bed to the intracardiac infusion of acetylcholine was lost after an interval of 40 months.

Materials and methods

Catheterization of the right side of the heart and cannulation of the brachial artery were performed with the patient in the basal postabsorptive state employing standard techniques. Cardiac output was determined by the direct Fick method and by the indicator-dilution technique employing indocyanine green.

The clinical data in Patient M. J. Hol were published previously, together with the results of the first cardiac catheterization in 1959. In the 40-month interval since the initial study, she noted easy fatigability, progressive exertional dyspnea, and dizziness. Recurrent febrile episodes had appeared.

On physical examination in 1962, the blood pressure was 160/88 mm. Hg and the heart rate was 90. No evidence of heart failure was noted. The cardiac point of maximum impulse was outside the midclavicular line in the fifth left intercostal space. The second pulmonary sound was markedly accentuated and was followed by a Grade 2 diastolic blow. A systolic ejection click was observed at apex and base. A right ventricular pulsation was felt in the fourth left intercostal space to the left of the sternum. At the pulmonary area, a systolic pulsation was present; the closure of the pulmonary valve was palpable. The fluoroscopic and electrocardiographic data remained unchanged and revealed marked right ventricular hypertrophy. The clinical impression was idiopathic pulmonary hypertension, cor pulmonale, enlarged heart, normal sinus rhythm, Graham Steell murmur, Class

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Table I. Hemodynamic data

	1959	1962
Pulmonary arterial pressure (mm. Hg) at rest, control	65/31, 43	98/46, 58
Pulmonary arterial pressure at rest during acetylcholine	45/26, 35	96/47, 61
Pulmonary arterial pressure, exercise, control	89/39, 55	
Pulmonary arterial pressure, exercise, during acetylcholine	53/26, 35	
Brachial arterial pressure at rest, control	140/75, 101	150/89, 116
Brachial arterial pressure at rest during acetylcholine	138/73, 96	141/81, 111
Brachial arterial pressure, exercise, control	170/90, 125	
Brachial arterial pressure, exercise, during acetylcholine	156/85, 117	
Acetylcholine infusion rate (mg./min.), rest	4.25	5.6
Acetylcholine infusion rate, exercise	4.25	
Cardiac index at rest, control	1.72	1.36
Cardiac index at rest during acetylcholine	1.87	1.37
Cardiac index, exercise, control	2.23	
Cardiac index, exercise, during acetylcholine	2.47	
Oxygen consumption (per M.²) rest, control	91	94
Oxygen consumption (per M.²) rest, during acetylcholine	93	97
Oxygen consumption (per M.²) exercise, control	175	
Oxygen consumption (per M.²), exercise, during acetylcholine	193	

II C. Medication included oral digoxin 0.25 mg. daily and oral Priscoline.

The cause of recurrent febrile episodes remained obscure until a diagnosis of systemic lupus erythematosus was established by multiple blood smear preparations which demonstrated lupus erythematosus cells. The administration of 10 mg. of prednisone daily controlled the clinical manifestation of the systemic collagen disease. Catheterization of the right side of the heart and the infusion of acetylcholine (5.6 mg. per minute) into the right atrium were repeated at this point.

Results

The control pulmonary and brachial arterial pressures were 98/46, mean 58, and 150/88, 116 mm. Hg, respectively. Right ventricular end-diastolic and right atrial pressures were 5 and 4 mm. Hg, respectively. Cardiac index equaled 1.36 L./min./M.² by the Fick method and 1.41 by the dye-dilution technique. Stroke volume was decreased to 38 ml. per beat. Arterial oxygen saturation, pH, and pCO_2 were 95 per cent, 7.44, and 34 mm. Hg, respectively. None of these data was significantly altered by the intracardiac infusion of acetylcholine at 5.6 mg. per minute. Table I summarizes the hemodynamic data obtained in 1959 and 1962. A satisfactory pulmonary artery wedge pressure curve was not recorded during either study.

Nitrous-oxide-inhalation studies (50 per cent nitrous oxide inhaled for 30 seconds) together with integrated simultaneous pulmonary and systemic arterial sampling (from 10 to 30 seconds of the period of inhalation of nitrous oxide) both in 1959 and 1962 were within normal limits and failed to reveal an intracardiac or extracardiac left-to-right shunt. Indocyanine indicator-dilution curves in 1962 also failed to reveal a left-to-right shunt. The latter curves were recorded simultaneously from the pulmonary and systemic arterial beds after injection into the right atrium and from the right atrial and systemic arterial beds after injection into the pulmonary artery. On the other hand, despite normal control arterial oxygen saturations (95 per cent) at rest during both studies, indocyanine-dilution curves in 1962 revealed a small but definite right-to-left shunt after injection into the right atrium (but not into the right ventricle) with sampling from the brachial artery. Right atrial mean pressure was normal at this time (4 mm. Hg), but the peak of the right atrial a wave reached 16 mm. Hg. The small right-to-left right atrial shunt was attributed to the pressure level of the a wave in this chamber.

Discussion

In our experience the intracardiac infusion of acetylcholine has resulted in clinically significant pulmonary vasodilation only in patients with primary pulmonary hypertension. The corresponding results in patients with rheumatic heart disease and cor pulmonale[9] have been disappointing in our hands.

In a prior study in 1959 the intracardiac infusion of acetylcholine resulted in a sharp decrease in pulmonary arterial pressure both at rest and during exercise in the patient whose data are outlined in this report. The development of progressive pulmonary vascular disease over the 40-month interval between the two catheterizations resulted in a further elevation of the pulmonary arterial pressure with a loss of vasodilator reactivity to intracardiac acetylcholine. This is the first case known to the authors in which such a phenomenon has been demonstrated.

The relationship between the pulmonary hypertension and systemic lupus erythematosus is problematical. Baehr and associates[10] described vascular lesions in the systemic and pulmonary beds of patients with systemic lupus. Pleural and intrinsic pulmonary involvement have been described in patients with lupus but extensive involvement of the pulmonary vascular bed with resultant hypertension is unusual. Smith and Kroop[12] have described 3 patients with a diagnosis of primary pulmonary hypertension in whom Raynaud's phenomena were present. It was postulated that a similar neurohumoral mechanism was responsible for the pulmonary hypertension and for the vasoconstriction in the extremities. Little evidence is available in the literature for a causal relationship between systemic lupus and severe pulmonary hypertension.

Summary

A follow-up case report of primary pulmonary hypertension is described. In 1959 intracardiac infusion of acetylcholine resulted in a considerable decrease in pulmonary arterial pressure both at rest and during exercise. In 1962 acetylcholine failed to elicit a decrement in pulmonary arterial pressure, demonstrating a loss of vasodilator reactivity of the pulmonary vascular bed over this period of time.

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Atherosclerosis in the mesenteric circulation
Observations and correlations with aortic and coronary atherosclerosis

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Clinical as well as anatomic interest in atherosclerosis has focused mainly on organs such as the heart and brain in which an embarrassed circulation causes a high morbidity and mortality as well as defined clinical syndromes. The paucity of similar features clearly referable to circulatory impairment of the abdominal viscera, and the vastness of the vascular bed in this area are some of the reasons why mesenteric atherosclerosis has been neglected both from a clinical and from a pathologic point of view.

Maljatzkaja, in a study of the abdominal visceral arteries which comprised 85 cases in the age range of 3 to 85 years, noted that, with the exception of the splenic artery, there was a tendency for atherosclerotic plaques to be concentrated in the dorsal portion of the circumference of the vessel and in the vicinity of branches. She observed the earliest (fatty) changes in the superior mesenteric and celiac arteries at age 20, in the splenic, (gastro) hepatic and inferior mesenteric arteries at age 38, and in the gastroduodenalis at age 42. In general, there was a correlation between the frequency of involvement of a given vessel and the chronological onset of atherosclerosis, i.e., the more often a vessel was affected by atherosclerosis the younger the age at which (lipid) plaques were first observed. On the other hand, the frequency of atherosclerosis in a given vessel did not necessarily coincide with its severity. The main stems were involved first and then progression of the disease took place in a distal direction and into the branches. There was a rough parallelism between the degree of atherosclerosis in the abdominal visceral arteries and the abdominal aorta. Maljatzkaja did not observe any cases of severe mesenteric atherosclerosis without severe aortic disease, although the reverse situation was noted occasionally. She distinguished sharply between changes due to aging and atherosclerosis, in spite of their similar topographic distribution.

Other authors[2,3] have emphasized the relative frequency of intimal calcification in mesenteric plaques as well as the rarity of ulceration.

Lapiccirella and Weber,[4] impressed by

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the frequency with which digestive symptoms precede coronary artery disease made a comparative study between the gastromesenteric and coronary arteries. Without giving criteria of grading they reported simultaneous atherosclerosis in both vascular territories in 61 per cent of 235 patients who were 40 years of age and over.

The purpose of the present study was twofold: first, to determine the occurrence of atherosclerosis in the arborizations of the celiac, superior mesenteric, and inferior mesenteric arteries and second, to compare the severity of atherosclerosis in these three arborizations with that of the coronary arteries and of the abdominal aorta.

Materials and methods

The present report is based on the autopsies of 88 adults observed at Beth Israel Hospital, Boston, Massachusetts, and The Bronx Hospital, New York City. With the exception of 4 cases of intestinal infarction the cases were entirely unselected and largely consecutive.

The technique used in this study has been described previously. It consisted of *en bloc* removal of the abdominal viscera, injection of the celiac, superior mesenteric, and inferior mesenteric arteries (the "constituent arborizations") with a radiopaque mass of barium sulfate in gelatin, partitioning of the viscera in accordance with the distribution of the constituent arborizations, preparation of x-ray arteriograms, and dissection of the vessels with scissors.

The celiac, superior mesenteric, and inferior mesenteric arborizations are here viewed as the constituents of a circulatory unit referred to as the "mesenteric arterial circulation." Thus "mesenteric disease," "mesenteric occlusion," and similar generic appellations in the subsequent text refer to involvement of any or all of the three constituent arterial arborizations.

The mesenteric arterial bed was divided into 23 named arteries (Table I). The anatomic features of atherosclerosis were determined by naked-eye inspection of the intima and recorded by means of symbols upon tracing paper placed over the arteriograms. In the current analysis, mesenteric atherosclerosis is expressed by the following criteria: (a) Spread, i.e., the number of named arteries per case showing one or more atherosclerotic plaques regardless of any associated stenosis. (b) Extent, i.e., the number of intimal plaques regardless of any associated stenosis. For reasons inherent in the gross anatomy of atherosclerosis (size of plaques, confluence) this criterion is not to be taken as an exact figure but rather as a numerical indicator reflecting the extent of intimal surface affected. (c) Magnitude, i.e., the number of stenoses regardless of degree. (d) Degree of stenosis, i.e., the percentage reduction in the lumen of the vessel by atherosclerotic plaques as determined by anatomic dissection and by visual estimate on the x-ray films. This was expressed on a scale of from 1+ to 4+, whereby 1+ signified a reduction of 1 to 25 per cent, 2+, 26 to 50 per cent, 3+, 51 to 75 per cent, and 4+, 76 per cent and over. Complete occlusions were listed as such.

It was not feasible to distinguish between different types of atherosclerotic plaques (lipid streaks or spots, fibrous plaques, atheroma, and complicated lesions) to weight the criteria enumerated above or to employ the composite grading of atherosclerosis proposed by Gore and associates.

The 88 cases of the series were grouped according to the spread of atherosclerosis, i.e., the number of named arteries involved. This procedure yielded 5 groups of roughly equal sizes (Table II). In Group A (15 cases), 8 to 23 arteries were affected; in Group B (18 cases), 5 to 7 arteries; in Group C (14 cases), 3 to 4 arteries; in Group D (21 cases), 1 or 2 arteries.* Group E (20 cases) displayed no plaques in any of the mesenteric arteries and served as a control.

There were 15 cases with one or more occlusions in the mesenteric arterial circulation, as follows: 9 in Group A, 4 in Group B, 0 in Group C, 2 in Group D, and 0 in Group E. For the evaluation of athero-

*Included in Group D is a 36-year-old man (A33-179) with mitral stenosis, auricular fibrillation, mural thrombosis of the left atrium and renal infarct. This case displayed a single point of stenosis at the orifice of the inferior mesenteric artery. Since there was no other sclerosis elsewhere in the mesenteric circulation (or in the aorta), the isolated point of severe stenosis was interpreted as recanalized thromboembolus.

Table I. Mesenteric atherosclerosis in 68 cases (Groups A to D) according to named arteries

Named arteries	I	II	III	IV				V	VI	VII	VIII
	Number of cases with atherosclerosis	Total number of plaques stenosing and nonstenosing	Number of cases with stenoses	Number of stenoses by degree				Total number of stenoses	Number of cases with occlusions	Mean diameter of artery§ (mm.)	Rank by length of artery‖
				1+	2+	3+	4+				
Superior mesenteric*	57	419	33	56¶	35¶	1	0	92¶	6	6.9	2
Splenic	48	538	24	41	52	7	0	100	4	6.5	3
Celiac	36	97	22	15	10	1	0	26	4	7.8	23
Inferior mesenteric	35	132	26	17	22	8¶	2	49¶	4	3.6	22
Gastrohepatic	25	63	6	10	1	[illegible]	0	11	1	5.9	—
Superior hemorrhoidal	22	81	14	15	7	1¶	1	24¶	4	2.8	—
Gastroduodenal	20	70	13	18¶	6	2	0	26¶	3	3.7	—
Ileocolic	15	54	8	8	10	5	1	24¶	4	3.7	4
Middle and accessory middle colics	13	58	9	10	27	12	1	50	5		5
Gastro-epiploics	13	67	6	9	7	10	0	26	4	—	1
Left gastric	13	24	5	2	3	0	1	6	2	3.9	—
Inferior mesenteric branches†	12	37	7	5	3	—¶	1¶	9¶	4	—	—
Enteric, third	12	22	5	3	2	0	0	5	2	3.4	7
Enteric, second	11	56	5	9	7	2	0	18	1	3.4	—
Enteric, fourth	10	19	6	5	3	—¶	1	9¶	3	3.4	6
Hepatic	10	39	6	6	6	0	0	12	1	4.5	—
Enteric, first	8	14	5	7¶	2¶	0	0	9¶	2	3.0	8
Enteric, fifth	8	15	4	2	3	0	1	6	2	3.1	—
Enteric, sixth	6	13	4	2	0	1	—¶	3¶	3	2.6	—
Pancreatic duodenal arcades	6	33	5	16	6	1	—¶	23¶	2	—	—
Right gastric	4	24	3	3	5	4	0	12	0	—	—
Enteric, seventh	3	5	1	0	0	0	—¶	—¶	2	2.5	—
Enteric, eighth seq.‡	3	4	1	0	0	0	1	1	3	—	—

*Main stem.
†Exclusive of superior hemorrhoidal artery.
‡Branches to small intestine distal to and including the eighth enteric artery.
§The mean diameters are derived from luminal dimensions as measured on the x-ray films after the vessels had been distended with radiopaque mass at 200 mm. Hg.
‖Longitudinal measurements of the mesenteric arteries are approximate since no uniform standard of termination of the vessels could be applied.
¶Denotes one or both of 2 cases in which narrowing was so extensive as to preclude counting of individual plaques. These 2 cases are omitted from numerical computation of stenosis in Columns IV and V.

sclerosis, the occlusions were disregarded because of their heterogeneous pathogenesis (thrombosis, embolism).

Coronary arteries. In connection with an unrelated study the coronary arteries were subjected to injection with a radiopaque mass, x-ray arteriography, and anatomic dissection. Atherosclerosis in the individual case was expressed only in terms of maximal degree of stenosis (1+ to 4+) or occlusion, using the same criteria as outlined above for the mesenteric arteries.

Abdominal aorta. Atherosclerosis of the abdominal aorta was estimated according to the area of intimal surface involved by plaques, ulcerations, calcification, and mural thrombosis. The identification of plaques was based on naked-eye inspection without the aid of Sudan stains. A scale of 0 to 4+ was adopted. [illegible] indicated no or negligible atherosclerosis, and 4+ indicated maximal involvement. No case with ulceration, thrombosis, or calcification received a grade of less than 3+.

Observations

Sex and age. The series comprised 43 men and 45 women who were between the ages of 28 and 88 years. The age distribution is recorded in Table III. The median ages were higher in Groups A and B, i.e., among the patients with advanced mesenteric atherosclerosis, than in those with lesser (Groups C and D) or no (Group E) mesenteric atherosclerosis. Similarly, the proportion of subjects who were 70 years of age and over was larger in Groups A (40 per cent) and B (44 per cent) than in Groups C (14 per cent) and D (24 per cent). Conversely, the proportion of subjects who were 50 years old or younger varied little among Groups A to D (7, 11, 14, and 14 per cent, respectively). In Group E, 20 per cent of the subjects were 70 years of age or older, and 35 per cent were 50 years or less.

Incidence of mesenteric atherosclerosis. In Table I the 23 named arteries are ranked in the order of frequency with which they were affected by atherosclerosis. The order differs only slightly from that which is obtained if the ranking is based either on the number of plaques ("extent") or on the number of stenoses ("magnitude"). Whichever criterion is employed, the vessels most prone to atherosclerosis were the superior mesenteric, splenic, celiac, and inferior mesenteric arteries. Noteworthy was the frequent involvement of the gastrohepatic, superior hemorrhoidal, and gastroduodenal arteries.

Extent and degree of mesenteric atherosclerosis. Among the 68 cases with mesenteric atherosclerosis, one or more of the plaques were stenosing in 49. For the majority of the named arteries, intimal plaques were associated with luminal stenosis in from one third to two thirds of the cases (Table I, Column III versus Column I). Among these 49 cases, narrowings of lesser degree (1+ and 2+) were vastly more numerous than those of higher degree (3+ and 4+). This may have been related in part to the generally large diameter of the mesenteric arteries involved. The mean number of plaques fluctuated greatly among the named arteries (Column II versus Column I), from 1 or 2 for the majority of the enteric arteries to 11 for the splenic. The propensity of the plaques to be of the stenosing variety was much greater in some vessels than in others (Column V versus Column II). For example, nearly all the plaques in the middle (and accessory middle) colic arteries were associated with stenosis, whereas only 1 in 6 plaques were so associated in the gastrohepatic artery. Finally, the mean number of stenoses per case (Column V versus Column III) was highest in such vessels as the splenic, gastro-epiploics, middle colics, and pancreaticoduodenal arcades.

The mean number of plaques per vessel showed no clear correlation with either the diameter (Column VII) or the relative length (Column VIII) of the vessel. When one considers the shortness of the celiac and inferior mesenteric main stems, these two vessels had the relatively largest number of plaques and stenoses per unit length.

The patients with nonstenosing atherosclerosis of the celiac, superior mesenteric, and inferior mesenteric main stems were younger (on the average by 3 to 6 years) than the patients with stenosing disease of the same vessels. The same was true for the splenic and gastroduodenal arteries but not for the left gastric or the superior hemorrhoidal arteries.

Topography of stenosis. Among the 49 cases with stenosing mesenteric atherosclerosis (occlusions being omitted from consideration), the main stems were involved in 44 cases as follows: celiac, 22 times; superior mesenteric, 33 times; inferior mesenteric, 26 times. Stenosis at the aortic ostia was present in 31 of the 44 cases, affecting one main stem in 14, two main stems in 9, and all three main stems in 8. However, in only 6 of these 31 cases were the stenoses confined to the aortic ostia, without additional stenoses in either the more distal portions of the main stems or in their branches. The incidence of stenosis at the ostia was greater for the celiac axis (19 of 22 cases, 86 per cent) than for either the inferior mesenteric main stem (19 of 27 cases, 70 per cent) or the superior mesenteric main stem (18 of 33 cases, 55 per cent). Of all the stenoses in the three main-stem arteries, one third (56 of 1[illegible]2) were located at their respective ostia.

Although ostial stenosis of the main-stem arteries might be presumed to be a

Table II Characterization of cases according to spread extent magnitude and degree of mesenteric atherosclerosis

Mesenteric athero-sclerosis Group	Number of cases	Number of arteries involved ("spread") Range	Number of stenosing plus nonstenosing plaques ("extent") Range	Median	Number of stenosing plaques ("magnitude") Median	Maximal stenosis ("degree") Number of cases† 0	1+	2+	3+	4+	Number of cases with stenosing plaques
A	15	8–23	24 194	62	21	0	0	4 2	8	2 2	15
B	18	5–7	10–52	32	4	2 1	1 1	9 2	1	1	15
C	14	3–4	4 33	10	2 5	5	3	5	1	0	9
D	21	1 2	1–12	3	0 5	9 2	6	3	0	1‡	10
E	20	0	0	0	0	20	0	0	0	0	0

*Two cases (A57 25 and A57-48) were omitted from calculation because the plaques were too numerous to count.
†The cases with occlusions in the mesenteric circulation are listed in boldface type. Note that the median of maximal stenosis is 3+ for Group A, 2+ for Group B, 1+ for Group C, and 0 for Group D.
‡Case A55-170; see footnote on page 201.

constituent part of coexisting aortic atherosclerosis the correlation between these two features operated more in one direction than in the other Although advanced atherosclerosis of the abdominal aorta (Grades 3+ and 4+) was present in all but 0 per cent of the 31 cases with ostial stenosis it was also present in 38 per cent (14 of 37) of the cases without ostial stenosis. Moreover there were 4 of 20 cases (20 per cent) in Group E in which there was advanced aortic atherosclerosis without even a single plaque in the mesenteric circuit

The propensity for stenoses in the branches of the three arborizations may be gathered from Table I Columns III and IV

Associated conditions of mesenteric atherosclerosis (Table III) The incidence of myocardial infarction both recent and remote declined with a decrease in mesenteric atherosclerosis, from 80 per cent in Group A to 38 per cent in Group D There was an incidence of 20 per cent in Group E. The prevalence of peripheral vascular disease (lower extremities) was considerably greater among the cases with severe mesenteric atherosclerosis than in those with lesser grades the incidence declined steadily from 47 per cent in Group A to 19 per cent in Group D There was an exceptionally high rate of diabetes mellitus among the cases of Group A (73 per cent) as compared with those of Groups B C and D Hypertension (systolic ≥ 170 mm Hg diastolic ≥ 90 mm. Hg or both) was decidedly more frequent in the cases with mesenteric atherosclerosis (Groups A to D combined) than in those without mesenteric atherosclerosis (Group E) and somewhat more so in Groups A and B than in Groups C and D

Correlations

Criteria of mesenteric atherosclerosis The group correlations between the number of named arteries involved by intimal plaquing (spread) the total number of plaques (extent) and the number of stenoses (magnitude) were quite good as was the correlation with the degree of arterial stenosis (Table II) This lends validity to our practice of utilizing th spread of mesenteric atherosclerosis as the yardstick of the disease and for the classification of the cases. Table II (Column *Maximal stenosis*) shows also that occlusions in the mesenteric arterial circulation have to be treated separately from stenosis whereas many of the occlusive cases (in boldface type) followed the correlative pattern of atherosclerosis, others did not, and for this reason alone these subjects are suspected of having acquired their occlusions by thromboembolism

Mesenteric versus coronary atherosclerosis With a decreasing spread of mesenteric atherosclerosis there was a progressive decline in the incidence of severe coronary atherosclerosis, from 73 per cent in Group

Table III. Distribution of cases by sex and age, together with incidence of myocardial infarction, peripheral vascular disease, diabetes mellitus, and systemic hypertension

	Mesenteric atherosclerosis group				
	A *(15 cases)*	*B* *(18 cases)*	*C* *(14 cases)*	*D* *(21 cases)*	*E* *(20 cases)*
Men (number of cases)	5	9	6	16	7
Age range	59–74	50–83	28–68	35–73	13–86
Age median	67	70	56	56	58
Women (number of cases)	10	9	8	5	13
Age range	28–88	46–78	53–75	53–72	39–82
Age median	64	67	60	62	57
Median age, both sexes combined	66	67	59	61	57
Myocardial infarction (%)	80	72	57	38	20
Peripheral vascular disease (%)	47	33	29	19	0
Diabetes mellitus (%)	73	22	13	6	5
Hypertension (≥170/≥90) (%)	64	3	45	52	22

*In several cases, pertinent information was unknown or uncertain. These cases are omitted from calculation.

Table IV. Distribution of cases according to spread of mesenteric atherosclerosis and degree of coronary atherosclerosis (by maximal degree of stenosis)

Mesenteric atherosclerosis group	*Number of cases*	Coronary atherosclerosis						*Per cent of 4+ and occlusive coronary atherosclerosis*
		0	*1+*	*2+*	*3+*	*4+*	*Occlusion*	
A	15	0	0	1 1	2	1 1	4 5	73
B	18	0	2	1	2 1	1	8 3	67
C	14	0	1	5	2	2	4	43
D	21	1 2	5	7	1	1	4	24
E	20	7	6	2	0	0	5	[illegible]

*Figures in boldface type denote cases with mesenteric arterial occlusions.

Table V. Distribution of cases according to magnitude of mesenteric atherosclerosis and degree of coronary atherosclerosis (by maximal degree of stenosis)

Number of mesenteric stenoses	Number of cases	Coronary atherosclerosis						Per cent of 4+ and occlusive coronary atherosclerosis
		[illegible]	*1+*	*2+*	*3+*	*4+*	*Occlusion*	
10 and over	15	0	[illegible]	1		1	6 8	80
4–8	17	0	1	4	2	3	3	59
1 3	17	1	1	4	3	0	7 1	47
0	19		6	6	1	2	2	21
No mesenteric atherosclerosis (Group E)	20	7	6	2	0	0	3	[illegible]5

*Figures in boldface type denote cases with mesenteric arterial occlusions.

A to 24 per cent in Group D (Table IV).* The pattern did not change materially (Table V) when the cases were grouped according to the number of mesenteric arterial stenoses ("magnitude"). Even when based on the (maximal) degree of luminal stenosis in both circulations, the correlative trend remained.

In summary, the data indicate that, depending on the criterion employed for the grading of mesenteric atherosclerosis, two thirds or more† of the cases with severe mesenteric atherosclerosis also had severe coronary arterial stenosis (4+ or occlusion). Conversely, of all the cases with severe coronary atherosclerosis in Groups A to D, only one third (11 of 34 cases) were found in Group A. In other words, the chances of severe mesenteric atherosclerosis being associated with either severe coronary arterial stenosis or occlusion was about 2 to 2½ times greater than the reverse association. Moreover, there was a fairly high incidence (25 per cent) of occlusive coronary atherosclerosis even among the control cases of Group E which were free of mesenteric atherosclerosis. In contrast to Groups A to D, the coexistence of coronary occlusion and of 4+ coronary stenosis in the cases of Group E was exceptional, thus conforming with the findings of Gore and associates that coronary occlusions (thromboses) can occur in association with even mild grades of atherosclerosis.

Mesenteric versus aortic (abdominal) atherosclerosis (Table VI). There was a progressive decrease in the incidence of severe (4+) aortic atherosclerosis from 60 per cent in Group A to 14 per cent in Group D (or from 100 to 29 per cent if Grades 3 and 4 of aortic atherosclerosis were combined). The correlation was quite similar when based on the number of mesenteric stenoses, but it became uncertain when based on the maximal degree of mesenteric stenosis. Whereas advanced (3+ and 4+) atherosclerosis of the abdominal aorta occurred not infrequently with little (Group D) or no (Group E) mesenteric atherosclerosis, no case with severe mesenteric atherosclerosis (Group A) had aortic disease of a grade less than 3+.

Aortic versus coronary atherosclerosis. The correlation between atherosclerosis of the coronary arteries and that of the (abdominal) aorta was fairly good (Table VII). Somewhat over two thirds of the cases with advanced (3+ and 4+) aortic atherosclerosis had severe coronary arterial disease (4+ stenosis and occlusion) also. Still, nearly one fifth of the cases with 3+ and 4+ disease of the abdominal aorta had minor (1+ and 2+) coronary atherosclerosis and about one tenth of the cases with minor aortic disease (0 and 1+) had severe coronary atherosclerosis.

Discussion

In a study similar to the one presented here, Maljatzkaja ranked the mesenteric arteries according to the incidence of atherosclerotic involvement as follows: superior mesenteric, celiac, splenic, gastrohepatic, inferior mesenteric, gastroduodenal, and branches of the superior mesenteric. Although the precise order differs between the two studies (just as it did in our own when ranking was based on the number of plaques rather than on the number of cases; see Table I), both surveys are in agreement relative to the leading involvement of the superior mesenteric, splenic, celiac, and (gastro) hepatic arteries. Both sets of observations differ from those of Kümmel, who found the celiac artery to be heading the list. Ferrari,[8] in a study which was confined to the celiac arborization, found the order of involvement to be as follows: splenic, celiac main stem, hepatic, left gastric. This conforms with our data (Table I).

No single common denominator appeared to account for the relative prevalence of atherosclerosis among the various named arteries (Table I). There were disruptive exceptions for each of the following variables: length of vessel, mean diameter, and distance from the aorta. Nonetheless, each of these variables seemed to exert some influence. That proximity to the aorta played a role is suggested by the

*The incidence figures remained essentially the same when the occlusions were disregarded and the correlation was based on 4+ stenoses alone, the reason being that the majority of cases with coronary occlusion also had 4+ stenoses.

†Seventy three per cent if based on *spread* of mesenteric atherosclerosis (Group A), 80 per cent if based on *magnitude* (10 or more points of stenosis), and 60 per cent if based on *degree* (3+ and 4+ stenosis).

Table VI. Distribution of cases according to atherosclerosis in the mesenteric arteries and in the abdominal aorta

Mesenteric atherosclerosis group	Number of cases	Atherosclerosis of abdominal aorta					Per cent of atherosclerosis of abdominal aorta	
		0	1+	2+	3+	4+	4+	3+ and 4+
A	15	0	0	0	3 3	3 6	60	100
B	18	0	1	3 1	5 1	5 2	39	[illegible]
C	14	1	0	3	4	4	29	59
D	21	0	5 2	8	3	3	14	29
E	20	1	14	1	2	2	10	20

*Figures in boldface ... to denote cases with mesenteric arterial occlusion.

Table VII. Distribution of cases according to atherosclerosis of the coronary arteries (by maximal degree of stenosis) and of the abdominal aorta

Atherosclerosis of abdominal aorta	Number of cases	Coronary atherosclerosis						Per cent of 4+ and occlusive coronary atherosclerosis
		0	1+	2+	3+	4+	Occlusion	
4+	23	0	2	2	3	4	14	72
3+	21	0	0	4	3	0	14	67
2+	18	1	5	7	1	2	2	21
1+	20	9	4	4	1	0	2	10
0	4	1	2	0	0	0	1	25

leading involvement of the three main stem arteries by the frequency of stenoses at the aortic ostia of these vessels, and by the observation that both stenosing and nonstenosing plaques in the superior mesenteric main stem were usually concentrated in and often confined to its proximal 9 to 12 centimeters.

The exceptionally high incidence of atherosclerosis in the splenic artery, a vessel which does not arise directly from the aorta, is noteworthy. Although the splenic artery does not lead the list in terms of frequency of involvement, it does so in terms of number of stenoses (Table I). With regard to the relationship, if any, between its propensity to elongation and tortuosity on the one hand and atherosclerosis, on the other, it is noteworthy that there were cases of splenic artery tortuosity in which there was little or no atherosclerosis. Maljatzkaja found atherosclerosis to affect the whole length of the splenic artery without showing the diminutive trend toward the periphery that is characteristic of other arteries of the mesenteric circuit. However, she stated that the most proximal segment tended to be relatively spared, becoming involved much later, less frequently, and to a lesser degree.

The incidence of mesenteric atherosclerosis in the current series was unexpectedly high: it affected 68 of the 88 adults (77 per cent) studied. In 49 of the 68 cases (72 per cent) the disease was of the stenosing variety. These findings do not appear to be fully explained by either the age distribution or the association with diabetes and hypertension (Table III). Although Group A, comprising the subjects with severe mesenteric atherosclerosis, was one of the oldest of the series, there was the equally impressive fact that one of the most severe cases of mesenteric atherosclerosis was observed in the youngest member of that very group, a 28-year-old

diabetic and hypertensive woman. Conversely, there was a juvenile and hypertensive diabetic patient in Group C, a 28-year-old man who died of uremia from recurrent pyelonephritis, whose mesenteric arborization displayed only inextensive atherosclerosis although the aorta showed 4+ atherosclerosis. Finally, there were some old individuals with established diabetes who had little or no mesenteric atherosclerosis.

Although the incidence of systemic hypertension declined with decreasing severity of mesenteric atherosclerosis, the differences between Groups A, B, C, and D were not impressive. This relative independence of mesenteric atherosclerosis from hypertension seemed to be genuine and not the expression of associated influences (Table III) such as diabetes mellitus or myocardial infarction with subsequent reduction in blood pressure. Even though hypertension was substantially less frequent among the subjects free of mesenteric atherosclerosis (Group E), it was still present in almost a quarter of these.

The possible clinical significance of stenosing disease in the mesenteric arborizations has been touched upon in connection with 15 cases of this series previously reported, in which in addition to stenosing atherosclerosis one or more occlusions were displayed also. These cases are identified in the tables in boldface type. Among the other 34 of the 49 subjects with stenosing but nonocclusive mesenteric atherosclerosis, no abdominal symptoms were encountered which could not be explained adequately by coexisting nonvascular pathology (peptic ulcer, gallbladder disease, carcinoma, hernia) or by chemical intoxication (lead, hexamethonium) with the possible exception of 3 subjects in Groups A and B. In these 3 individuals, maximal mesenteric stenosis was 2+, and the otherwise unexplained abdominal symptoms included pain, distention, and guaiac-positive stools. It is possible, of course, that in some of the seemingly asymptomatic patients, and especially in those with 3+ and 4+ mesenteric stenosis, symptoms of circulatory impairment had in fact been present but were not recorded in the clinical protocols. If so, the failure of recording may indicate that chronic encroachment on mesenteric arterial patency lacks both symptomatic specificity and clinical urgency, a matter which may be related to the large collateral potential inherent in the mesenteric circulation.[3]

The comparison between atherosclerosis of the mesenteric bed and that of other vascular units as presented in the body of this paper is open to criticism because of unequal criteria of grading. Notably with respect to coronary atherosclerosis, the single criterion of maximal stenosis (or occlusion) here employed for grading is not necessarily a good reflection of total intimal disease in the individual case. However, our own practical experience and that of others[12] suggests that, individual exceptions notwithstanding, the degree of luminal stenosis generally parallels other anatomic aspects of the severity of coronary atherosclerosis.

With these qualifications in mind, the present study has disclosed a substantial rise in myocardial infarction (Table III) and severe (4+ stenosis and occlusion) coronary atherosclerosis (Table IV) with increasing grades of mesenteric atherosclerosis. At the same time it was shown that the correlation tended to be one-sided in that a subject with advanced mesenteric atherosclerosis had a substantially greater chance of having also ischemic heart disease and severely stenosing coronary atherosclerosis than the reverse. This association may perhaps deserve consideration in the interpretation of abdominal symptoms in individuals who are suffering from ischemic heart disease. A one-sided relationship was also observed between mesenteric and aortic (abdominal) atherosclerosis showing that widespread mesenteric atherosclerosis (Group A) was always associated with advanced disease in the abdominal aorta, but that severe aortic atherosclerosis was often associated with little or no mesenteric disease. Moreover, whereas stenosis at the ostia of the mesenteric main stems was nearly always associated with 3+ and 4+ atherosclerosis of the abdominal aorta, it was uncommon to see such stenoses confined to the ostia. As to the correlation between aortic and coronary atherosclerosis, our observations closely parallel those reported by Glagov

and co-workers[13] in spite of differences in grading

Summary

The mesenteric arterial bed of 88 adults was analyzed for atherosclerosis according to the number of vessels affected, the extent of involvement of the intimal surface, and the number and degree of stenoses. The mesenteric bed, defined as comprising the celiac, superior mesenteric, and inferior mesenteric arborizations, was divided into 23 named arteries comprising the 3 main stems and their major branches. The series had a nearly equal number of men and women with an age range of from 28 to 86 years. Atherosclerosis in one or more of the 23 named arteries was found in 68 (77 per cent) of the cases. The vessels most frequently affected were the three main stems and the splenic artery. Also quite frequently involved were the gastrohepatic, superior hemorrhoidal, and gastroduodenal arteries. Among the 68 subjects with mesenteric atherosclerosis the disease was associated with luminal stenosis in 49. The majority of the stenoses were of mild to moderate degree. The propensity of atherosclerosis to be associated with stenosis varied considerably among the named arteries. Stenosing disease was particularly common in the main stems, occurring in 44 subjects, i.e., in 50 per cent of the total series or in 65 per cent of those with mesenteric atherosclerosis. Even though the aortic ostia of the main-stem arteries were often involved, it was rare for the stenoses to be confined to the aortic ostia.

The incidence of myocardial infarction rose significantly with the severity of mesenteric atherosclerosis, and this was true also, although to a lesser extent, for peripheral vascular disease. The incidence of diabetes mellitus was exceptionally high in the group with severe mesenteric atherosclerosis and was quite low in all other groups. Hypertension, although occurring rather frequently with mesenteric atherosclerosis, did not clearly correlate with the severity of the latter.

There was a good correlation between the severity of atherosclerosis in the mesenteric circulation and that in the abdominal aorta. The correlation, however, was one-sided, in that severe atherosclerosis of the abdominal aorta occurred not infrequently with little or no mesenteric atherosclerosis, whereas the reverse was not observed. A fairly good but similarly one-sided correlation was found between mesenteric and coronary atherosclerosis in that the chance of severe mesenteric atherosclerosis being associated with severely stenosing or occlusive atherosclerosis of the coronary bed was 2 to 2½ times greater than the reverse. Finally, there was a fairly good correlation between coronary and (abdominal) aortic atherosclerosis.

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Summary

The use of intracardiac epinephrine in the treatment of experimental cardiac arrest is described.

We have shown that the use of epinephrine, as an adjunct to artificial respiration and cardiac massage, is of great benefit in restoring spontaneous circulation. Epinephrine should be used in the treatment of both myocardial standstill and ventricular fibrillation.

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A hydrostatic pressure gradient in the pleural sac

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Analysis of the pressures in the pleural cavity is essential in the evaluation of transpulmonary pressure gradients and in the study of transpleural fluid movements.

At the turn of the century, Aron[1] observed that intrapleural pressure measured directly in man during resting expiration oscillated from −3 to −5 mm. Hg and that this pressure became lower as the subject assumed the upright position. Prinzmetal and Kountz[2] noted that in subjects in the lateral decubitus position the pressure in the dependent portion of the pleural cavity was 3 to 5 cm. of water higher than that in the elevated cavity. This finding was attributed to a shift of the mediastinum and diaphragm which reduced the size of the dependent lung and decreased its elastic recoil. Wiggers and associates[3] inserted air-filled needles into various parts of the pleural cavity of dogs and found end-expiratory intrapleural pressures to vary between −6 and −11 cm. of water. Fahri and associates, also using air-filled needles, found intrapleural pressures in supine dogs to be essentially unchanged between the third and eighth intercostal spaces; pressure in the apex was lower by 2 cm. of water, whereas that in the posterior gutter was higher by the same amount. It has been generally accepted that these slight variations in pressure in the pleural cavity may be due to the weight of the lung. Thus, Krueger and associates, finding a pressure gradient of 0.22 cm. of water per centimeter along the length of the pleural cavity in upright dogs, interpreted this as a "hydrostatic" effect of the lung, the density of which was calculated as 0.22.

In 1949, Buytendijk[4] documented the relationship between intraesophageal and intrapleural pressures. Thus, fairly consistent estimates of mean intrapleural pressure have been obtained with a long (15-cm.), narrow (2 cm. in diameter), partially air-filled balloon placed in the lower third of the esophagus. Variations in pressure observed on movement of the balloon to different segments of the esophagus have been attributed to regional differences in esophageal compliance and muscle contraction, and to compression by adjacent structures.

The present study suggests that some of

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	PRESSURE cm H_2O	DIFFERENCE IN HEIGHT cm M–N
M	−12	
N	−2	
M-N	−10	+10
M	−8	
N	−8	
M-N	0	0
M	−2	
N	−12	
M-N	+10	−10

Fig. 1. Method. The diagram illustrates 3 of the 9 positions in which the animals were placed. The differences in pressure may be compared with the differences in height between points *M* and *N*.

the discrepancies in the literature on intraesophageal pressures may be due to a gravitational intrapleural pressure gradient. Clarification of the magnitude of such a gradient may assist in the study of transudation of fluid into the pleural spaces and its resorption, as well as of the relationships between the transpulmonary pressure gradient, pulmonary compliance, and ventilation.

Materials and methods

1. Animal studies. Intrapleural pressures were measured in 8 pentobarbitalized (25 mg. per kilogram) dogs (15 to 20 kilograms). Saline-filled blunted No. 14 needles inserted in the third or fourth and the seventh, eighth, or ninth intercostal spaces were attached by means of three-way stopcocks to separate strain gauges which recorded on a two-channel Sanborn machine. To prevent the entrance of air into the thoracic cavity, a purse-string suture was placed around a 1-cm. incision in the skin, a needle was pushed through the muscle into the pleural space, and the skin was brought tightly around its shaft by tightening the suture; surgical jelly ensured an air-free seal between the shaft of the needle and the chest wall. The needles were flushed occasionally with less than 1 ml. of saline.

The two manometers were maintained at the same height. The height of each needle relative to its manometer could be determined at any time by opening the three-way stopcock to atmosphere. Measurements were made with the animal in 9 positions ranging from head-up to head-down (Fig. 1).

2. Studies in man. The effect of the position of the body on intraesophageal pressures was determined in 8 male subjects using three techniques. Technique I utilized a short (1.25 cm.) condom rubber esophageal balloon[8] 0.75 cm. in diameter with an unstressed volume of 0.65 ml. The subject, loosely strapped to an upright tilt table, leaned 5 degrees forward or was tilted to the prone position. The partially collapsed balloon (air volume less than 0.33 ml.) was introduced through the nose and passed into the stomach by means of an air-filled polyethylene catheter (internal diameter of 0.8 mm.). Pressures were recorded as in the animal studies described above as the balloon was withdrawn by 2-cm. increments to the hypopharynx. Technique II differed in that the polyethylene catheter was filled with saline and had an open tip. In Technique III the open-tip catheter was connected to a

Fig. 2. Hydrostatic properties of [illegible] flow of fluid. External pressure compresses segment X. Fluid level A may be raised to B or lowered to C, but flow through X equilibrates the new level with A. The time required for equilibration is proportional to the pressure compressing X. X is the difference in height that would have been observed if the height of the column X did not contribute to the hydrostatic balance.

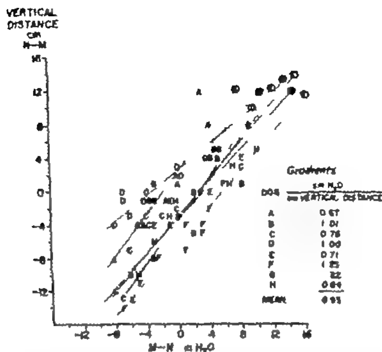


Fig. 3. The relationship between ertical distance between two needles (*M* and *N*) in the pleural space of the dog (*ord nate*) nd the pressure recorded from these needles (*abscissa*). Each letter refers to specific animal. Thus each *A* on the graph represents measurement. The line drawn through the data obtained from each nimal is identified by rcle around the letter ttached to the upper end of the line. The erage gradient for each nimal is given in the inserted table.

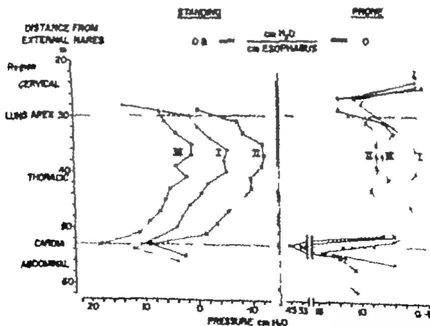


Fig. 4. Technique I. Balloon connected to a pressure transducer. Technique II. Saline-filled catheter connected to pressure transducer. Technique III. Saline-filled catheter connected to a standpipe manometer.

Table I. A comparison of the ratio of pressure/length in 12 esophageal studies on 8 subjects in the standing and prone positions

Subject	Age	Technique*	cm water/cm length	
			Standing	Prone
Normal				
R H	24	I	0 70	0
R H		I	0 72	–
R K	30	I and II	0 80	0 25
J G (heavy smoker)	33	I	0 45	0 30
J C (heavy smoker)		III	0 53	0
Emphysema				
J M	56	I	0 50	0 17
T G	66	I and II	0 33	0 18
A J	70	I	0 40	0 20
A J		III	0 66	0
J O	48	III	0 55	–
Mitral insufficiency				
K S (congestive failure)	64	III	1 00	0
K S (pleural effusion)		I II III	0 80	0
Average			0 62	0 11

*Techniques I, II, and III are described in Fig. 4

saline standpipe manometer constructed of the same tubing. Equilibration pressures were determined by allowing saline to flow freely from the manometer into the esophagus until the falling pressure in the manometer reversed during resting expiration. Determinations of pressure with the catheter were corrected for the height of the tip. Thus, the pressure in the manometer was relatively unaffected by movement of the catheter up or down the esophagus; the intraesophageal values were corrected by subtracting the values obtained when the saline filled catheter was at the same level in air; esophageal pressures were plotted against the length of the esophagus estimated on the basis of the length of the catheter.

3. Model experiments. An analogue was used to demonstrate pressure equilibration (Pascal's law) through a very thin column of fluid comparable to the intrapleural fluid (Fig. 2). A segment of one limb of a water filled glass U tube was replaced by commercially available flat cellophane tubing enclosed in a cylinder in which the extravascular air pressure could be controlled. The water-filled cellophane tubing was collapsed by raising the cylinder pressure to values higher than that of the column of fluid in the manometer. A variant of this experiment was carried out to show the effect of bubbles trapped in the column of liquid; the height of the bubble-containing arm of the U tube was compared with that of the opposite arm.

Results

Intrapleural pressures in the dog. Simultaneous pressures varied directly with the vertical distance between the points of measurement in the thorax of 8 dogs regardless of the position of the animal. The gradient varied from 0.67 to 1.25 cm of water per centimeter of vertical distance (Fig. 3) with an average of 0.93, approximately equal to a hydrostatic effect.

Esophageal pressures in man. The resultant gradients with the three esophageal pressure techniques were essentially identical for simultaneous measurements (Fig. 4). With the subject in the upright position the pressure gradient in the intrathoracic esophagus ranged from 0.4 to 1.0 cm of water per centimeter (Fig. 4) with an average of 0.66, which is less than was expected on a hydrostatic basis. The gradient was most apparent in the esopha

geal segment 5 cm. above the cardia to 5 cm. below the cervicothoracic junction.

Data on the 8 subjects are given in Table I. Although our data are insufficient to characterize the gradients in terms of various physiologic states, the largest gradient (1.0) was in Subject K.S. who had chronic congestive failure without pleural effusion secondary to fenestration of the mitral valve (verified at autopsy). Six months later, after development of a right pleural effusion but with a normal systemic venous pressure, the same subject showed a gradient of 0.8. A similar gradient (0.8) was seen in a normal subject. The gradient was eliminated almost entirely by tilting the subjects to the prone position (Table I).

Model experiments. The levels of fluid in the two arms of the air-free U tube approached a common value despite the fact that the cellophane segment was flattened by extravascular pressures up to 200 cm. of water; the time required for equilibration varied directly with the pressure applied to the outer wall of the cellophane tube. By contrast, the presence of air bubbles in one arm of the U tube resulted in a difference in the water level in the two arms which was almost exactly equal to the vertical length of the bubbles.

Discussion

The data obtained in experiments on dogs, in man, and with the analogue indicate that the thin column of fluid in the pleural cavity exerts a hydrostatic effect on its containing walls. Since the volume of pleural fluid is small and the close proximity of the pleural surfaces offers considerable resistance to flow, the effect can be demonstrated only by low-compliance manometers. Furthermore, the introduction of air bubbles into the sac may reduce or eliminate the hydrostatic effect. Thus the numerous clinical measurements in patients with pneumothorax fail to elicit a gravitational gradient. The gradient becomes manifest only when the above-noted precautions are observed.

The pressure gradient in the upright esophagus is significantly less than hydrostatic, perhaps because of varying esophageal tone[1, 13] and compression and distention of adjacent structures. Air bubbles above the balloon may also diminish the esophageal pressure gradient. It appears that the conventional (15-cm.) esophageal balloon has technical value in the estimation of changes in intrapleural pressure but provides no basis for the estimation of instantaneous intrapleural pressure gradients. The small air bubble in the balloon will always move to the point of lowest pressure and will reflect only the pressure at that point; this effect is demonstrated by introducing such an air-filled balloon into a beaker of water.

The intrapleural pressure gradient balances the hydrostatic gradient in the pulmonary veins. These vessels, which lie immediately under the visceral pleura, would generate a transmural gradient of as much as 30 mm. Hg from elevated to dependent portions were it not for the intrapleural pressure gradient. Such an intra-

Table II

	Intrapulmonary air pressure	*Pleural pressure*	*Pleural minus intrapulmonary (transpulmonary) pressure*	*Capillary pressure*	*Capillary-pleural pressure gradient*
Elevated	0	−20	−20	5	23
Mid-high	0	−15	−15	10	23
Hilar	0	−10	−10	15	23
Dependent	0	− 5	− 5	20	[illegible]
Critically dependent	0	0	0	25	23

This table assumes intrapulmonary air pressure to be uniform. In conditions in which constriction of the airways is not uniform, the resulting intrapulmonary air pressure differences may modify the values given.
*The lung will tend to collapse because of intra-alveolar surface forces when the transpulmonary pressure gradient approaches zero.

pleural pressure gradient and a uniform air pressure on the other side of the visceral pleura would result in a transpulmonary pressure gradient maximal at its most elevated segment. The effect of such a gradient on the measurement of compliance of the lung appears to merit further study.

It may be suggested for example that the introduction of a pneumothorax will eliminate the pleural hydrostatic column and thereby result in an unbalanced pressure gradient in the extrapulmonary vessels. The change in fluid balance may affect patterns of transudation of fluid into and resorption from the pleural space.

During expiration transpulmonary pressure approaches zero in the most dependent portions of the lung. This increases the likelihood that the surface forces operative in the alveoli and bronchioles can bring about collapse of such a dependent segment. The increasing transpulmonary pressure during inspiration and positive pressure breathing probably counteracts this tendency to collapse.

Setnikar and associates have suggested that the subatmospheric pressure in the pleural sac results from the continuous osmotic absorption of fluid by pleural capillaries. The pressure gradient which we have observed probably cannot be accounted for on the basis of difference in osmotic pull since both intrapleural and capillary pressures must increase equally with depth; the hydrostatic forces across the capillary membrane would then be equal at all levels and absorption from the pleural space would occur over the entire lung surface. Conversely, a critical rise in pulmonary venous pressure may produce transudation across the entire pleural surface with the formation of an effusion. These relationships are suggested in the hypothetic values given in Table II.

Summary

Pressures at various sites in the pleural cavity were measured directly in dogs and estimated from intraesophageal pressures in man. The results show that intrapleural pressure increases with dependency essentially according to a hydrostatic gradient. These results are discussed in terms of the effect of such an intrapleural pressure gradient on esophageal pressure, the production and resorption of pleural fluid, transpulmonary pressure, and the ventilation of various elevations of the lung.

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Measurement of right ventricular volume by cineangiofluorography

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It is usually assumed that the outputs of the two ventricles are perfectly balanced, but the possibility that there are moment-to-moment differences in ventricular outputs and in the ejection patterns has been difficult to test because of the absence of a suitable method for following change in the volume of the individual ventricles in intact animals. In recent years, two approaches have emerged: one depends on the installation of flowmeters in the pulmonary artery and aorta, and the other requires cinevisualization of the contours of the ventricular chambers. Using the flowmeter approach, Franklin, Van Citters and Rushmer[1] were recently able to compare and contrast right and left ventricular ejection patterns very precisely. Using a similar method, Guz and co-workers compared stroke volumes of the two ventricles as well as flow patterns in the aorta and pulmonary artery.

The following report deals with the development of a technique that employs the morphologic, or cine, approach. In the case of the *left* ventricle, it has proved to be possible in recent years to follow change in its volume in intact animals and human beings by use of biplane cinefluorography. The technique furnishes a series of direct measurements of ventricular volume at rates of 15 to 30 per second over 3 to 10 consecutive cardiac cycles. From such volume curves, stroke volume can be directly measured.

The biplane cinefluorographic technique is applicable in the case of the left ventricle because of the relatively regular, approximately cylindrical shape of the chamber. The right ventricle, because of its highly irregular contour, presents a very different problem. It is a relatively thin, flat chamber which partly envelopes the left ventricle. The anatomic relationship between the two ventricles is depicted in Fig. 1, in which the thin, crescentic right ventricle appears to be applied to the septal wall of the left. Some of the functional implications of the arrangement were described in 1953 by Rushmer, Crystal and Wagner, whose work also shows that the volume of the interventricular septum is quite large with relation to the volumes of the chambers.

The volume of a chamber shaped like the right ventricle obviously cannot be determined by the method developed for the left ventricle. It is possible, however, to determine total ventricular as well as left ventricular volumes. Both ventricles, taken together, have a conoidal shape and can be dealt with geometrically. All this being

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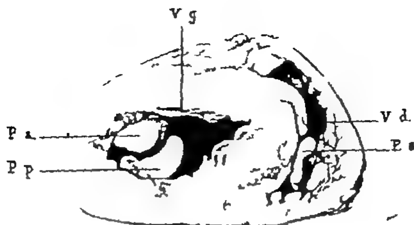


Fig. 1. Cross-section through the human heart at mid ventricular level. (From Marc See.) V.g. Left ventricle. V.d. Right ventricle. P.a. Anterior papillary muscle. P.p. Posterior papillary muscle.

true, one should be able to estimate right ventricular volume simply by subtracting left from total ventricular volume provided that allowance can be made for the volume of the interventricular septum.

The concept, expressed as an equation and diagrammatically, is set forth in Fig. 2. The volume of the right ventricular cavity (R) is obtained by subtracting the sum of the volumes of the interventricular septum (S) and the left ventricular cavity (LV) from the total ventricular volume (T).

Method

The technique for determining left ventricular volume was described in full in 1958. It requires the simultaneous cineangiofluorographic recording of two views of the opacified chamber at about 90 degrees to each other and rests on the assumption that the cross-sectional outline of the ventricle is elliptical or circular.

In practice, anesthetized dogs were suspended before the two cinefluorographic cameras by means of a special body sling in as natural a position as possible. The position usually employed provided right and left anterior oblique views of the canine heart. Injection (into the right atrium) was by means of a pneumatic injector of the Rodriguez-Chavez Dorbecker type. Contrast medium was a 90 per cent solution of diatrizoic acid salt (Hypaque-M) and the dosage was 0.5 ml. per kilogram. The usual x-ray settings for the dog studies were 120 kv. and 150 ma. at 30 frames per second. Film records usually extended over 6 to 10 seconds, and care was taken to obtain the desired temporal relationship between injection of radiopaque medium and the beginning of the film record. After the filming, the dog was removed and a lead reference standard was suspended in the position previously occupied by the heart. A short film was made of it (in both planes) for use in correcting distortion due to divergence of x rays.

The most laborious part of the procedure then followed. Twin 35-mm. still projectors

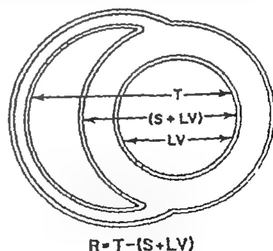


Fig. 2. Diagram of cross-section of ventricles, showing measurement used in the calculation of volumes of the ventricles. T: Total volume of the two ventricular cavities and the septum. S + LV: Septal plus left ventricular volume. LV: Left ventricular volume. R: Volume of the right ventricular cavity.

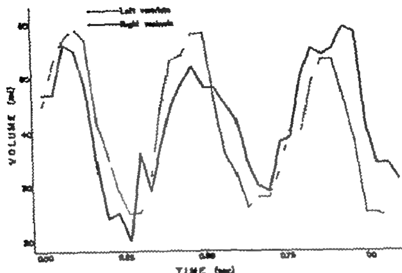


Fig. 3. Right and left ventricular volume curves in normal dog.

were set up side by side so that the projected image was reflected by front-surface mirrors without distortion or loss of clarity onto a horizontal surface below. The height of the projectors was adjusted so that the filmed images of the reference standard corresponded precisely in size to the actual standard. Each of the simultaneously recorded 35-mm. film strips was then numbered (every tenth frame) and put into one of the 35-mm. still projectors. Two operators, one for each view, traced corresponding frames simultaneously, frequently comparing shapes and boundaries as they proceeded. A 16-mm. movie projector loaded with a loop of the appropriate 16-mm. reduction print (both views) was placed so that both operators were able to view the movie version as well as the still conveniently and frequently. The importance of using the movie version as a reference while the stills are being traced cannot be overemphasized. Without it many obscure lines and borders are either misplaced or overlooked entirely. This is especially true of valve planes. The images for each corresponding pair of frames were traced at precisely the same level on specially slotted roller paper. When the tracing was complete, the roll was fed into a scanner-computer described in a previous publication. The instrument measures diameters in corresponding tracings (right and left anterior oblique) at 1 mm. intervals from top to bottom and the computer calculates volume of successive 1 mm. horizontal sections of the ventricular cavity according to the following equation

$$V = \frac{h\ (AA \times BB)}{4}$$

where h = thickness (1 mm.), AA = diameter in left anterior oblique view in mm. and BB = diameter in right anterior oblique view in mm. at the same level as AA. Total ventricular volume for each thirtieth of a second (each pair of frames) is obtained by summing all the volumes of the 1-mm. sections and is printed by the machine on paper tape.

The error of the method as judged by experiments with ventricular models and various cylindrical test objects is relatively small. From these data, the method appears to overestimate left ventricular volume by an average of 1.4 per cent, but may, once in 20 tries, overestimate it as much as 16 per cent or underestimate it as much as 13 per cent.

For measurement of right ventricular volume the same instruments and principles were employed. Injection was in two stages; the first preceded the second by 2 to 4 seconds. About 15 ml. of contrast medium was injected at each stage. The technique has the effect of permitting the first bolus of dye to opacify the left ventricle before the second bolus opacifies the right ven-

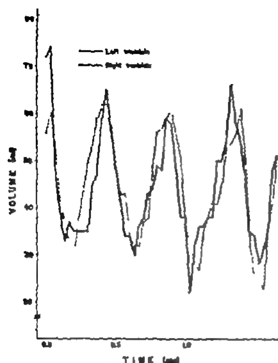


Fig 4 Right ad left entricular olume curves in normal dog showing respiratory effect and tendency of right entricula ejection t begin earlier than left

tricle After both stages are accomplished both ventricles are made visible for several cycles.

The 35-mm. negative images were then traced on special slotted paper as before Three series of biplane tracings were necessary the first was of both ventricular cavities together the second was of left ventricular ca ity with septum and the third of left ventricular cavity alone The tracings were then fed into the scanner computer and the three sets of volumes were calculated The values were inserted into the equation given in Fig 2 [R = T − (S + LV)] which yielded right ventricular volume for each thirtieth of a second

Results

The results show that in general right and left ventricular volumes are of similar but not identical magnitude during the cardiac cycle Fig 3 shows superimposed volume curves of the right and left ventricles over 3 cardiac cycles. Right ventricular volume is indicated by the solid line and the left ventricular volume by the dashed line In the first cycle the end diastolic volume of the left ventricle is larger than that of the right ventricle, but in the second cycle the values are about the same. Stroke volume differs very little between the cycles. Also right ventricular emptying usually begins earlier than left but sometimes is later Similar features are seen in Fig 4 The effect of respiration is particularly plain in Fig 4. In these and most other studies, right ventricular ejection usually lasted slightly longer than left ventricular ejection

Discussion

Instant to-instant differences between right and left ventricular volumes were inferred by Katz[7] from simultaneously recorded pressure curves. Mean values based on a number of consecutive cycles, however differed very little The present study yielded similar results (Table I) although pressures were not measured Franklin and co-workers[1] were able to characterize ejection patterns much more precisely because their technique permits recording under many conditions and for long periods of time. They show that right ventricular ejection usually begins earlier and lasts longer than left ventricular ejection. The present results are mostly in agreement. Franklin and colleagues also show that right and left ventricular ejection patterns usually respond to stress simultaneously but that under abnormal conditions they may be 180 degrees out of phase. From these and other results it appears likely that a combination of the two methods for following ventricular activity may yield still further information of value.

Also of interest in the present study is the relatively large size of end-systolic

Table I Mean values for right and left ventricles in 10 normal dogs (3 to 5 cycles each)

	Right ventricle	*Left ventricle*
End-diastolic volume (ml.)	44 ± 9	44 ± 11
End-systolic volume (ml.)	19 ± 8	19 ± 7
Stroke volume (ml.)	25 ± 7	25 ± 6
ESV/EDV × 100	41 ± 12	43 ± 10
Septal volume (ml.)	13.5 ± 3.2	

Average weight of 14.2 kilograms.

(residual) volume under the circumstances of the experiments. Complete emptying of the ventricles has never been observed with the cinefluorographic method even during simulated exercise

The volume of the interventricular septum appears to be unduly high possibly because of its location shape, or geometric artifact. However it can usually be seen quite readily and in any case possesses a sizable volume.

Summary

A method for measuring the volume of *both* ventricles in dogs over several cardiac cycles is available it demonstrates significant differences, from moment to moment in ejection patterns of the two ventricles but confirms the fact that stroke volumes are usually identical The volume of the interventricular septum was found to be relatively large at rest it amounts to about 50 per cent of the stroke volume under the conditions of the experiments.

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Studies in cerebral circulation
Methods for the qualitative and quantitative study of human cerebral blood vessels

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The blood supply of the brain has been studied since the time of Galen. Although the relationships of the major vessels, especially the components of the circle of Willis, are well known, the spatial arrangement of the intracerebral vessels relative to sources of supply is not clearly defined.

Because of difficulties inherent in the processing of human materials, methods devised for the study of cerebral blood vessels have been largely confined to the in vivo injection of experimental animals. Vital dyes and other injection media have been used. The comprehensive studies of Craigie,[5a] Pfeifer,[7] and Cobb[3] have provided valuable information concerning the arrangement and number of intracerebral blood vessels. Similar studies in man are scarce, especially in regard to regional angioarchitecture and relative numbers of cerebral capillaries in various diseases.

Our knowledge of the anatomy of the cerebral circulation in man has come primarily through injection studies. Many have been meticulously executed and have utilized multicolored injection media to delineate regional areas of supply. There is no question that within the pia-arachnoid there are numerous interarterial anastomoses,[7] and that major branches of the circle of Willis are interconnected at their peripheral zones of supply (Beevor, 1907). In 1872 Cohnheim[4] devised the concept of "end arteries" as an explanation of the pathogenesis of infarction. This idea has been retained although the studies of Pfeifer,[7] Craigie,[5a] Cobb,[3] and others establish the presence of a rich anastomotic network between adjacent capillary fields. According to Pfeifer, there are no "end arteries" in the brain. Much of the confusion concerning this subject lies in the meaning of terms. If the term "end artery" implies an arterial blood vessel without connections with other arterial vessels, Pfeifer's interpretation is correct. Here the term "arterial" apparently denotes functionally related vessels and does not restrict intercommunications to size. Thus, no "end artery" exists in Pfeifer's concept, since all supplying arteries are interconnected at the arteriole and capillary level.

The Cohnheim concept refers to the absence of anastomotic connections be-

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tween arteries of relatively large size, which if present would provide blood to a given capillary field from several peripheral loci. Thus, it appears that, although an extensive and protective anastomotic network is present at the capillary level adjacent fields of hemispheric supply are only anastomotic within the pia-arachnoid. In addition Gillilan described arteriovenous anastomoses in the pia. For these reasons, injection methods using colored media might lead to incorrect conclusions in regard to specific areas of supply especially if injection pressures were unphysiologic or a large blood vessel was nearly or completely occluded by an atheromatous plaque.

The use of plastic or neoprene injection media requires destruction of the specimen by subsequent digestion techniques. Although these methods have proved to be excellent for certain organs, the loss of cerebral parenchyma makes interpretation of the resulting arterial cast difficult since the relationships of the cast relative to supporting tissue and nuclear groups are lost. Complete injection of the human cerebral vascular tree with viscous media requires high perfusion pressures which produce numerous artifacts; lower injection pressures cause incomplete filling.

Many investigators have used India ink or colored media to delineate specific areas of supply. One classic study that dealt with the regional distribution of specific branches of the circle of Willis in man was done by Beevor[1] (1907). He simultaneously injected various segments of the circle of Willis with multicolored dyes. Many dyes are unstable and fade with time or during subsequent histologic processing, whereas others discolor the specimen and alter staining reactions.

The purpose of this paper is to describe a modified injection procedure which permits the study of the three-dimensional arrangement of cerebral blood vessels without alteration of the gross or microscopic characteristics of the specimen. In addition it provides a photographic record of individual sections for stereoscopic study of injected intracerebral blood vessels in the serially sectioned human brain. Improved quantitative methods are presented which make possible the estimation of capillary volume relative to the cyto-architecture and volume of cerebral tissue.

The descriptions that follow are based on injections of 138 normal and pathologic human brains from subjects who ranged in age from 7 months to 92 years. This collection of material forms the nucleus of an extensive study concerning the components of the circle of Willis as well as the distribution of specific blood vessels in the normal brain and in the brain altered by primary disease of the blood vessels. Procedures for the study of capillary structure and intracerebral angioarchitecture are also described. These are presented along with preliminary results as illustrative examples. It is hoped that the methods described and illustrated may be adopted for the study of the cerebral angioarchitecture relative to pathologic states out of the scope of this research.

Materials and methods

One hundred thirty-eight human brains were similarly processed except when numerous leaking arterial vessels and/or lacerations of the cortex made adequate injection impossible.

Injection method. The unfixed brain was injected arterially through four cannulae tied into the internal carotid and vertebral arteries. These cannulae were PE 260 polyethylene tubing connected by means of adapters and pressure tubing to a reservoir bottle that contained the injection mass. Compressed air was supplied to the bottle via a 5-gallon pressure drum controlled by a regulator valve and a mercury manometer. Acceptable injections were more frequently obtained if the brain was less than 12 hours post mortem and fewer artifacts (blowouts) occurred when perfusion pressures were below 100 mm. Hg.

After cannulation the cerebral vessels were flushed by syringe to test for leaking vessels; these were ligated. While distended with saline, each component of the circle of Willis was measured for diameter. The circles were evaluated as to symmetry and deviations from the so-called adult pattern were noted. The cannulated brain was supported by a

cloth sling in running water or floated in hypertonic saline solution, the specific gravity adjusted so that the specimen just submerged. Residual blood was flushed out with saline solution, followed by an injection medium that consisted of 20 per cent Micropaque in 10 per cent formalin. Attempts to harden, using 20 per cent formalin, were made prior to injection but produced unpredictable results and had to be abandoned. The quantity perfused varied from 200 to 600 c.c. of Micropaque in 10 per cent formalin. In general, the degree of filling could only be estimated by the appearance of the finer vessels of the pia and the amount of venous leakage. Particle size was less than 1 micron, so that both arteries and veins filled. Subsequent to injection, the brain was fixed for 7 to 10 days in 20 per cent formalin solution and then was washed in running water for 24 hours. The most troublesome factor was the presence of intracerebral extravasation of the injection medium. These artifacts were seen most frequently in the centrum ovale. Frequently, the smaller arteries were occluded by clots which prevented adequate filling; attempts to rectify this fault were made by using hypertonic saline, dextran solutions, saponin, and saline or solutions containing 3 per cent gelatin as flushes prior to injection with Micropaque. None of these methods gave consistent results; many produce edematous changes and are not recommended. In our experience, 10 per cent formalin proved to be the best vehicle for the injection mass, and the process partially hardened the brain, producing better fixation.

Sectioning. The construction of three-dimensional stereograms of injected blood vessels from serial sections requires that adjacent sections be equal in thickness and parallel. In addition, x-radiation of sections should be of uniform density, since soft x-rays are required for the study of the finer vascular radicals. These requirements are difficult to fulfill "freehand" without the use of some device for the support of both the specimen and cutting edge, together with a method for the uniform advancement of the cut surface. Such a device is illustrated in Fig. 1. It consists of a simple box which measures 9 by 9 by 11 inches inside; a false bottom forms a movable floor. The arrangement for elevation consists of a threaded brass screw 12 inches long and ¾ inch in diameter. This screw passes through a threaded flange fastened in the center of the bottom and supports the false bottom. Thread pitch (25 threads per inch) advances the false bottom 1 mm. per turn. The upper end of the macrotome is fitted with parallel bars of stainless steel ⅜ by ⅜ by ½ inch. These are inlaid in grooves ⅛ inch deep and serve as a flat surface for the support of the knife. The knife that provided the best results measured 50 cm. long, 5 cm. wide, and 7.5 mm. thick at the back.

The camera is a 16-mm. Paillard Bolex movie camera, with a Switar 25-mm. lens, bolted to the table top over the macrotome. This arrangement provides for the photographic recording of selected serial sections without variation in alignment of the optical axis relative to the specimen.

Embedding procedure. Routine coronal sections were made by orienting the brain vertically in the macrotome, utilizing a removable brass rod which formed a support in the plane between occipital lobes and cerebellum. Holes drilled in the side (*H*, Fig. 1) position this rod in the horizontal plane. Support in the mid-sagittal plane is provided by a similar rod (*S*) which passes obliquely through the front of the macrotome near its top so as to extend slanting downward toward the genu of the corpus callosum in the longitudinal cerebral fissure.

The embedding medium consisted of 15 pounds of Plastico moulage,* cooked in a double boiler until liquid and then cooled to 100°F. or less. This was poured over the brain, completely filling the box, and allowed to solidify overnight. When solid, the moulage provided a firm supporting substance which sectioned easily and also served as a contrasting background. The orienting rods were removed and serial sections cut from 1 mm. to 5 mm. by appropriate advancement of the screw. Sectioning was done by simply resting the knife flatly and firmly on the guides and sliding it across with uniform pressure.

*The moulage is an artist's negative mold material obtained from Sculpture House, 38 East 30th St., New York 16, N. Y.



Fig. 1. A photograph showing the arrangement for sectioning and photographing brains. A partially cut section of brain is seen protruding out of the top of the macrotome. *S* and *H* indicate the holes for positioning the sagittal and horizontal supporting rods.

The blade was kept wet with water. In general, sections from 3 to 5 mm. thick proved to be the most desirable for the radiologic study of injected blood vessels.

As each section was cut, the enclosing moulage was peeled away and the section placed on a piece of cellulose acetate, 5 by 7 inches, with the number of the brain and section marked in the lower right-hand corner. The cut surface was photographed using approximately 2 feet of Kodachrome A film and the embedded brain was elevated for the next section. Sections were stored on numbered acetate films in plastic boxes containing 10 per cent formalin solution.

X-ray procedure. The x-ray equipment used was a Model 6191 Picker industrial machine, provided with a thin beryllium window rated at 50 kv. 7 ma. Other sources of soft x-rays could be used equally well, such as the dermatologic therapy machine used by Prolo and Stillwell (1960). Before being x-rayed, sections were blotted dry and placed on clean pieces of acetate. Acetate film of this thickness (.005 inch) is radiolucent. Lead numbers identified each section. The sections were centered below the tube port over 5 by 7 inch Kodak fine grain positive film without cassette. The safe light used contained a Wratten 1A or OA filter illuminated by a 15-watt bulb. Exposure time for 4-mm. sections was 3 minutes at 26 kv. and 6 ma., port 12 inches from the film. Development time was 3 minutes in Dektol solution diluted 1:2 with water at 68°F. This procedure provides a negative film of high contrast and fine grain which can be enlarged using conventional equipment.

The preparation of x-ray stereograms is accomplished as follows. The section is x-rayed twice, each film is angled 3 degrees from the axial ray on an inclined platform. This platform is a rectangle of ½-inch plywood that measures 6 by 8 inches, provided with a narrow cleat ⅜ inch thick nailed to the under surface of one end. The section is x-rayed first with the cleat on the left, then is x-rayed again using a new film with the cleat rotated 180 degrees (or on the right). A stereoscopic view of injected vessels is provided when enlarged prints of these x-ray films are examined through a stereoscopic viewer.

Although the use of contact roentgenograms is not new, greatly enlarged positive projection prints of such films are quite effective for the tracing of vessels through comparatively large areas of sections up to 5 mm. thick. These methods of course cannot be expected to produce enlargements comparable to those obtained by Saunders with a projection x-ray micro-

*U. S. Army magnifying stereoscope manufactured by Fairchild Aviation Corp.



Fig. 2. (For legend see bottom of opposite page.)

scope but they have the virtue of being less expensive. It should be mentioned that colored slides made with a 35-mm reflex camera are satisfactory substitutes for movie film and have the advantage of being reproducible for publication purposes.

Histologic preparations. For routine study specific areas of the injected brain were selected from a survey of the contact roentgenogram. Blocks were excised and sectioned at 150 microns using a freezing microtome thinner sections were alternately cut for combined staining techniques designed to illustrate capillary neuron relationships. The staining procedure used for blood vessels was developed in the laboratory of Courville[4] by Mahoney. This method provides reliable color fast stains of high contrast and resolution. Thinner sections, 50 to 100 microns, were similarly stained and then counterstained with Nissl's method. Routine paraffin sections were prepared for the purpose of identification of specific arterial vessels, as seen in the roentgenograms.

Relative vascularity of the cerebral cortex. Many methods have been devised for the study of the relative vascularity of the cerebral cortex. Counts of neuron nuclei provide some measure of the population density of neurons in various cortical areas. In general these methods express the former in terms of capillary length in microns per cubic millimeter of cerebral tissue the latter in terms of nuclei per unit volume. The literature contains such terms as capillary loops and arcades. These terms are misleading since there are few true capillary loops in the human brain. In addition, measures of vascularity are gross approximations based upon the summation of lengths of injected capillary many of which appear in thin

Table I. Estimated values of relative vascularity of the human cingulate gyrus

	Human cingulate gyrus		
	Cortex	*Junctional white*	*Semiovale*
Whole weight of paper			
Area of optical plane (85,800μ^2)	868 mg	780 mg.	870 mg
Weight of capillary cutout	210 mg	90 mg.	48 mg
Per cent capillary vascularity	24%	11%	5%
Tissue volume	$5.3 \times 10^6\mu^3$	$5.3 \times 10^6\mu^3$	$8.2 \times 10^6\mu^3$
Number of neurons	60	—	—
Capillary volume	$1.27 \times 10^6\mu^3$	$0.58 \times 10^6\mu^3$	$0.21 \times 10^6\mu^3$
Capillary length	$16 \times 10^3\mu$/mm.	—	—
Values of relative vascularity as reported by authors cited			
Craigie[6]			
(Converted volume—$5.3 \times 10^6\mu^3$)	$0.157 \times 10^6\mu^3$	—	—
Cobb[3]	2,370μ/mm.	—	—
Dunning and Wolff[10]	4,500μ/mm.	—	—

Fig. 2. Top. A photomicrograph illustrating one optical plane used in preparing stereogram. Depth of optical plane is 4 microns. Silver stain; magnification ×430. The dimensions of the tissue observed can be calculated using the micrometer scale at the lower left of each illustration (1 division = 10 microns). Numbers identify those neurons in the stereogram which are in relative focus at the 12-micron optical level of section. These are also identified numerically in the photomicrograph above. A precapillary arteriole (*A*) supplies the three-dimensional capillary rete. The clear space around this vessel, crosshatched in the stereogram, is the perivascular space of Virchow Robin. Bottom. Stereogram compiled from tracings of 14 consecutive optical sections. A precapillary arteriole (*A*) is seen crossing obliquely in both illustrations. Crosshatching outlines Virchow Robin space. The capillary net consists of branched anastomotic vessels approximately 10 microns in diameter. Numerals indicate neurons in focus at the 12-micron level. Thickness 56 microns. Scale divisions are [illegible] microns. Magnification ×430.

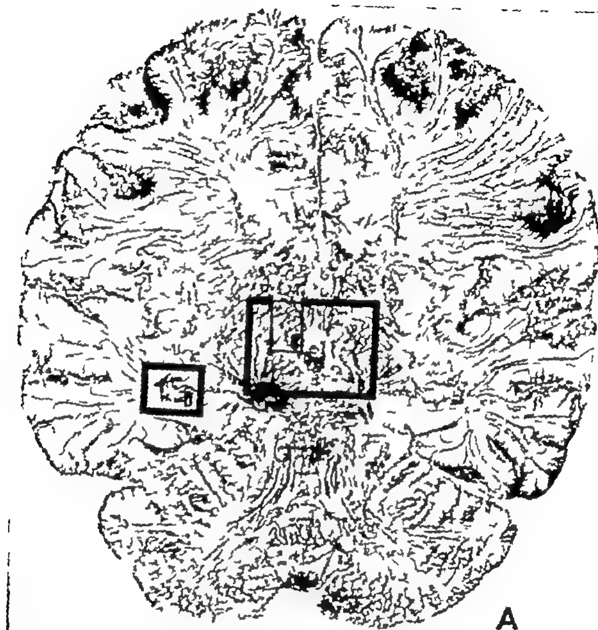


Fig. 3 The ... pr ... of ... me ... n ... film ... f a ... ronal sect on 4 mm ... h k par llel to the longitud nal ... of the br ... m. M ... m ×1. Clear ... re ... on each side of he midl ne and in the center represent the position of he ... erior hor ... of he la er l entricles and the third entricle respecti ely. The pineal body is the round dark mass ... l low he third ventricle. F ... med ... ea B, C, nd D indic ted are enlarged a Figs. 4, 5, nd 6.

sections as curved vessels. These method are inaccurate ther f re and ... el l values which are t o mall. W it ut the use of a perimeter arc len th canno t be a urately estimated.

Errors also arise because the microsco-pi t is forced to count nd me ure many vessels in one fiel l; this increases the hance f either neglecting a few or measur ng several vessels more than once. Because the method relies on the injection l ap llaries w th dye only injected vessel are seen nd although complete njection in an mal materials i fairly e y to accompl I, imil success with the hu nan brain is very l fficult to attain.

For these reasons another method was devised for the quantitative measurement of differential capillary volume. This method uses the principle of serial optical planes of section of uniform thickness. The stereogram is a two-dimensional scale reconstruction compiled from serial photographs through successive optical sections. The following procedure is recommended. Areas of the cerebral gray matter are selected for study, and frozen sections cut at 50 to 100 microns. These are doubly stained for blood vessels and neurons using the Mahoney silver and Nissl stains. The area to be reconstructed is serially photographed, each photograph cutting an optical focal plane 4 microns removed from the preceding plane. This is accurately done by advancing the vernier calibration of the microscope fine adjustment. The stereogram is compiled from the serial photographs and is constructed as follows.

The photomicrograph of the first optical plane, which is the uppermost focal level, is covered with a clear glass plate. Those vascular elements in sharp focus are traced onto the plate, and the plate is registered on the next photomicrograph (next lower optical plane). This process is repeated until all optical planes have been transferred to the plate. Conventional methods of reconstruction are complex, and difficulty often arises when accurate registration of successive levels is attempted. When structures are curved in various planes, accurate registration of successive levels is not possible, since there are no two fixed points in constant relation to one another that can be used as guides. This problem is easily solved by holding the optical axis of the camera constant relative to the area photographed, i.e., the fields photographed are not changed in the planes perpendicular to the optical axis. When enlarged prints are made, the



Fig. 4. Area *B* of Fig. 3 enlarged. The complex vascular supply of the pineal body (*P*) is seen in the center of the radiograph. The cerebral peduncles and the externally peduncular circulation are just inferior to the pineal gland. The arrow points to *apparent* anastomoses between the striate arteries (*A*). Magnification ×5.25.



Fig 5 Area C of Fig 3 larged Portion of the distributions of triat rteries (*A*) are ll l trated Area X enclosed l tippling, ppears to be the sular supply to a entral thalamic ucleus. The gray ba kground is due to capillary filling To the left of the curved tippled l ne lies the medial part of the globu pallid s. Between the stippled area is the clearer less scular internal caps le (*I*). The crosshat hing and the area at n lt show the supply t thalamic nuclei dorsally M gnification × 17

right-hand and lower borders of th e nega tive serve as convenient and constant axes on which to regi ter the glass transfer plate on succes ive photomicrographs.

The photomicrograph at the top of Fig 2 illustrates one optical plane the third of a series of 14 *consecutive optical* planes each 4 microns apart The resultant

stereogram compiled from tracings of the entire series of photomicrographs is illustrated at the bottom of Fig. 2.

Measurement of the relative capillary and cortical areas of the stereogram can be made using various graphic methods. The technique employing paper weight per standard area is simple and reproducible, provided that the paper is of a type resistant to absorption of atmospheric water, transparent, and of uniform thickness. From the glass transfer plate, the outlines of blood vessels are traced onto ordinary draftsman tracing paper. The outlined capillary vessels are cut out and weighed. Capillary area is simply derived from the weight of the cutout, relative to the weight of a piece of similar paper of known area.

There are certain errors inherent in the measurement of aggregate capillary area and volume by the method described. The initial assumption in regard to the construction and measurement of stereophotomicrographs requires that all vessels which appear in relative focus at each optical lamination of the stereogram be projected onto the plane of the first optical

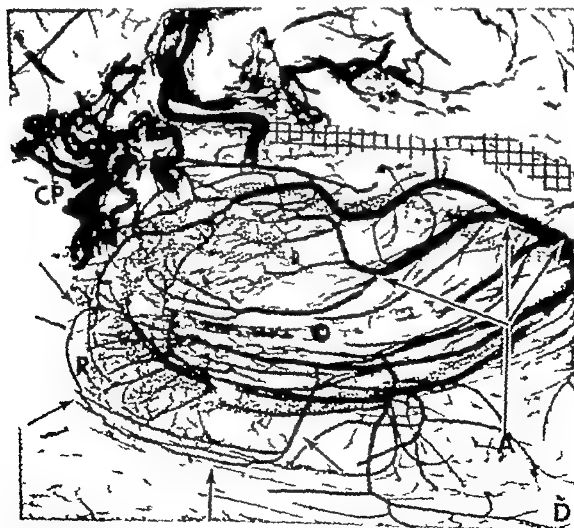


Fig. 4. Area *D* of Fig. 3 enlarged. Microcirculation of the hippocampus and dentate gyrus. Crosshatching overlies the region of the ... The stippled area (*D*) represents the lamina pyramidalis. The arrows point to branches of the choroidal artery (*A*) which pass to the left, apparently forming ... in the ... *R*, *C* label ... partly filled ... Magnification X12.



Fig [illegible] Enlargement showing the rich vascular supply of the pineal body The diffuse d rk rea just below *P* is lcareous deposit Magnification X 16 5

level This produces an error in the relative length of all blood vessels oblique to the plane of the stereogram If the ratio of the area in the plane of the stereogram is relatively large *compared to the area at* right angles to the stereogram this error is minimized The method is reproducible with a total error of approximately 10 per cent and allows for the differential identi fication enumeration and study of all cyto-architectural layers of cerebral gray *matter in relation to capillary* angio-architecture.

Table I lists measurements of the total

capillary rete illustrated in Fig 2 calculated to give absolute values for capillary volume relative to tissue volume.

Capillary volume represents approximately 24 per cent of total tissue volume, or 1.27×10^{4} cubic microns and 5.29×10^{4} cubic microns respectively The stereogram illustrates the capillary rete as a three-dimensional lacework of anastomotic vessels. Capillaries measure approximately 10 microns in diameter and 1 neuron is related to approximately 370 microns of capillary length To our knowledge these expressions of relationship between capillary and neuron are new

For comparison Table I also lists indices of relative capillary vascularity according to Craigie[26] Cobb[3] and Dunning and Wolff[1] These indices were originally expressed in terms of capillary length in microns per cubic millimeter (Cobb[3] Dunning and Wolff[1]) and capillary length in microns per 7.22×10^{8} cubic microns of cortex (Craigie[26]) For purposes of comparison the authors have modified these measurements to standardize the dimensions. Our measures of capillary volume are nearly 10 times those calculated from Craigie s data. Capillary length values are about 4 times those of Dunning and Wolff and 8 times those reported by Cobb These differences are due in some part at least to the fact that the authorities cited measured different areas of the cerebral gray in the rat cat and rabbit In addition the method used was, in each case designed to give a relative index as to vascularity no attempt was made to express values in absolute terms. Perimetric methods for measurement of arc length were not used

Estimated measures using these methods of capillary reconstruction approach more nearly the values calculated for the size of the cerebral reservoir Estimates of the cerebral reservoir based upon per cent capillary volume (24 per cent) relative to the volume of the cerebral gray yield values compatible with those estimated using dye-dilution techniques. Nylin reports a cerebral reservoir of 130 c.c as measured using labeled red blood cells and values ranging from 90 to 180 c.c. have been reported by others.

If the mean volume of the human brain is assumed to be approximately 1 000 c.c. and entirely composed of gray matter the cerebral capillary reservoir would be approximately 240 c.c. If it were entirely myelin this reservoir would contain 50 c.c. Although these figures are gross approximations, they are of the right order of magnitude, and it may be presumed that the true value lies somewhere between these limits (mean value 140 c.c.)

Results

Fig 3 is a positive print of a contact x-ray film of a paracoronal section through the human brain This section is oblique inclined anteriorly 30 degrees to the coronal plane and parallel to the longitudinal axis of the brain stem Without magnification the intracerebral vessels show up in high contrast to the surrounding parenchyma. Subfigures labeled alphabetically refer to subsequent enlargements of specific areas of this section This series illustrates the high degree of resolution obtainable with the method. Preliminary descriptions in regard to the three-dimensional arrangement of certain intracerebral blood vessels are also presented.

Fig 4 illustrates a higher magnification of the area labeled *B* in Fig 3 The pineal gland (*P*) appears in the center and branches of the striate arteries are indicated (*A*) The arrow shows an area in which the striate arteries seem to be anastomotic above the capillary level This apparent interarterial anastomosis was not confirmed by stereoscopic examination of this area and the presence of interarterial anastomoses between vessels of this size has not as yet been observed

Fig 5 illustrates at higher magnification part of the distribution of the striate artery (*A*) The area circumscribed with stippling and labeled X indicates its apparent zone of distribution. It is to be noted that the interstices between the specific branches of this artery are darker than elsewhere in the illustration This darkening reflects capillary filling in a central thalamic nucleus. To the left of the region marked Y is another stippled area. This is the medial aspect of the globus pallidus. The circulation of the thalamic nuclei dorsally is outlined by crosshatching These areas surround a

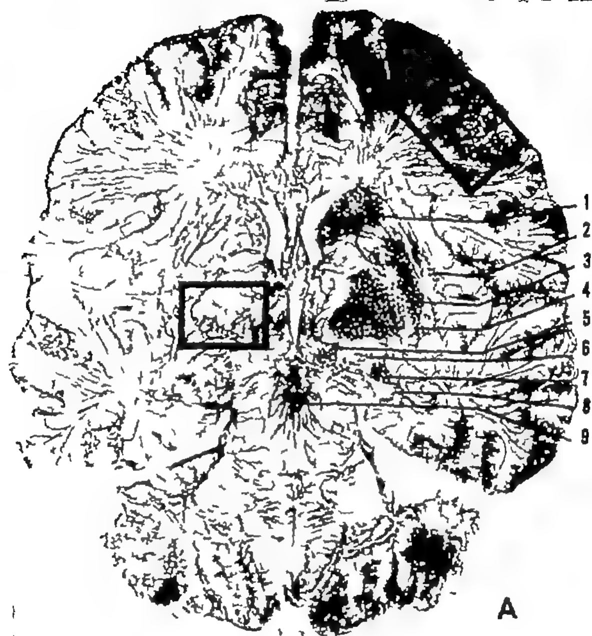


Fig. 4. [illegible] genogram. Section 4 mm. thick, 10 degrees paracoronal plane. Magnification ×1. Key: stippled [illegible] (1) [illegible] nucleus, (2) claustrum, (3) putamen, (4) globus pallidus, (5) red nucleus, (6) medial geniculate [illegible] (7) lateral geniculate body, (8) location of choroidal artery, (9) interpeduncular [illegible]scular plex. Framed [illegible] B orient. location of Fig. 9. Framed area C orient. location of Fig. 10.

central relatively uninjected zone (*I*) the internal capsule and corona radiata.

Fig. 8 illustrates the microcirculation of the hippocampus and dentate gyrus (area *D*, Fig. 3). The crosshatched zone denotes the region of the alveus. The stippled areas (*D*) denotes the position of the lamina pyramidalis. The three arrows at the bottom point to blood vessels which can be seen to originate from elements of the choroidal artery (*A*) in the right center of the illustration. If followed toward the left, branches of this vessel (*arrows*) seemingly anastomose, forming apparent arcades in the region labeled *R*. The partially filled vessel illustrated in the center (circle *C*) is a draining venous channel.

Fig. 7 represents an enlargement of the



Fig. 9. Area *B* of Fig. 8 enlarged. Shows blood supply of globus pallidus (*GP*) enclosed in stippling; the putamen (crosshatched area *P*) injected poorly. Magnification ×5.

Fig. 10. Cortical arteries and veins of the first order are present. At the extreme left of the illustration a sulcus has been cut across showing arteries passing through it supplying the cortex and sending branches into the underlying white matter. On the right a cortical artery (*A*) sends right-angled branches into the subcortical fiber tracts. A partly injected vein (*V*) is outlined. Its tributaries and branches of the arteries require histologic examination for definite identification. Magnification ×4.

injected pineal gland The pineal circulation is elaborate and arterial and venous filling is nearly complete

Fig 8 is a print of a contact roentgenogram The section is through the plane of the caudate nucleus (*1*) and globus pallidus (*4*) lateral geniculate body (*7*) and interpeduncular fossa (*9*) These numerically designated areas were stippled in for orientation Of particular interest is the arrangement of arteries and veins lateral to the caudate nucleus (*1*) Here these blood vessels course in parallel arcades between fiber bundles of the forceps minor fanning outward from the apices of the anterior horn of the lateral ventricles Examination of the white matter elsewhere in this section shows this arrangement to be characteristic Histologic examination confirms the fact that most of these vessels are arteries. Between the putamen (*3*) and the caudate nucleus (*1*) on the right is a large blood vessel this is part of the striate system within the internal capsule Similar blood vessels are seen on the left When traced serially they are found to originate from perforating branches from the lenticulostriate complex of the lateral part of the anterior perforating substance These are apparently end arteries, for stereoscopic evaluation has failed to show the presence of interarterial anastomoses above the capillary level

Arterial blood vessels of similar arrangement are noted in the interpeduncular fossa (9) the floor of which is perforated by end arteries which branch from the terminal portion of the basilar artery and adjacent vessels

Fig 9 presents an enlarged view (*B* Fig 8) that shows the blood supply to the globus pallidus and putamen The arterial vessels are small and are located within the stippled areas delineating the globus pallidus (*GP*) The dotted line marks the boundary between the outer and inner zones of the globus pallidus and bisects two blood vessels which run parallel to it The cross hatched area *P* above the globus pallidus did not inject The blood vessels form a more or less framing network that bounds this portion of the corpus striatum and are arteries the specific identity of which was confirmed by subsequent histologic study The three-dimensional arrangement of blood vessels in this area leaves little doubt that the circulation is highly organized around the neurons forming the lentiform complex The presence of interarterial anastomoses, miliary aneurysms, and detailed information concerning the arterial supply and venous drainage are of primary importance relative to functional concepts of this major part of the extrapyramidal system The details of angioarchitecture in this region of the normal human brain are not clearly understood the microcirculation in disease is virtually unknown

An enlargement of the vessels of the cortical pia mater is presented in Fig 10 (area *C* Fig 8) The cortical surface is nearly parallel to the plane of the illustration Three frontal gyri are present. On the left are two gyri cut at right angles to their long axes the third is sectioned in the long axis and is angled upward and to the left of the figure. Above this region the pia flattens so that incident x rays are perpendicular Here numerous pial arteries form a rich anastomotic network. The large cortical vein (*V*) was incompletely injected On the right hand side the smaller radicals of the pial arteries (*A*) are illustrated These send perforating blood vessels into the substance of the cortical gray matter Many traverse the white matter without obvious branching to course parallel to the fiber tracts beneath Some of these vessels are veins some are arteries.

Fig 11 (*A* and *B*) illustrates low power and high power views of selected areas adjacent to the lateral ventricle in the region of the centrum semiovale These vessels branch from pial arteries coursing through the gray into the white matter parallel to the fibers of the corona radiata and forceps. It is re-emphasized that with x-rays alone one cannot always distinguish arteries from veins. The accepted criteria have been uniformity of size method of branching and termination when traceable The identification of an arterial or venous blood vessel on the basis of these criteria alone is risky Fig 11,*A* illustrates two types of arterial blood vessels which conform to these criteria Arrow *a* points to an artery of essentially uniform diameter which when

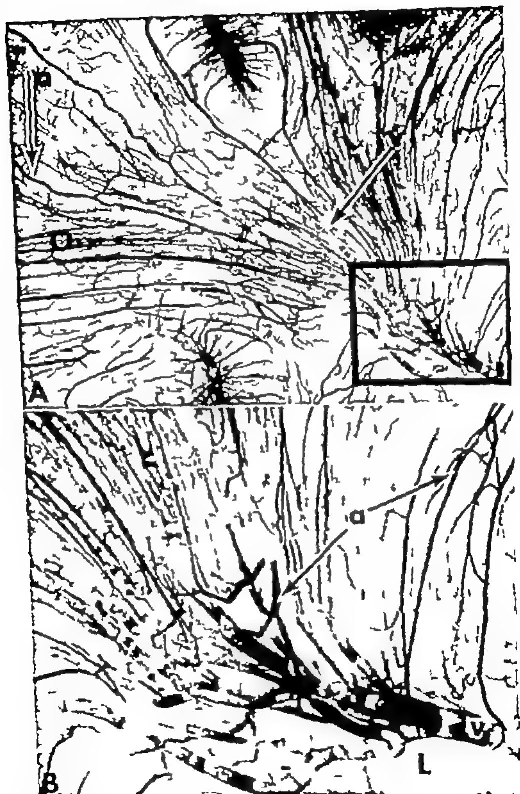


Fig. 11. *A*, Cortical arteries ( ) and veins ( ) converge upon the lateral angle of the lateral ventricle. Magnification ×4. *B*, Magnification of the terminal part of the above veins as they drain into the subependymal plexus of the lateral ventricle (*L*). Accompanying cortical arteries (*a*) are seen. Magnification ×11

traced toward the lower right branches progressively into vessels of diminishing diameter. The circle circumscribes another variety of arterial blood vessel which is unbranched and coiled, forming a loose spiral. This spiraling may be seen along the entire length of the vessel or may be segmental and is seen more often in the brain of the elderly. Histologic observation confirms the identity of these vessels as arteries, and the spiraling is often associated with collections of perivascular macrophages. The significance of these observations is not clear. Arrow v points to a partially filled blood vessel of uniform diameter. Its termination is in a system of similar blood vessels within the circumscribed area labeled *B*. Fig. 11,*B* magnifies this region. Here it is noted that there are several blood vessels of rather large diameter which have converged at the upper lateral aspect of the lateral ventricle (*L*). These blood vessels are of relatively uniform size and, on the basis of established criteria, would appear to be arterial blood vessels. Subsequent histologic examination of this area showed these vessels to be mixed. Those partially filled are predominantly veins, whereas the smaller completely filled vessels are arteries (*a*). The terminus of venous drainage is in the subependymal venous circulation.

Summary

Injection of 138 normal and pathologic human brains has led to the development of standardized methods for the comprehensive study of cerebral blood vessels. A device for the rapid parallel sectioning of the whole human brain at 1 to 5 mm. is described. Modified x-ray techniques are presented which provide for the stereoscopic study of intracerebral arteries and veins without destruction of the specimen or alteration of staining properties. Procedures for the quantitative study of capillary angioarchitecture in normal and pathologic brains are presented and methods for the differential study of vascularity in absolute terms are described. Preliminary observations are used as illustrations.

We wish to thank Charles Dunlap, M.D., Professor and Chairman of the Department of Pathology, and his staff for their cooperation in providing the necessary anatomic materials.

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Case reports

Primary sarcoma of the mitral valve

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Primary cancers of the heart although rare are of unusual interest. They are seldom suspected before death which in most cases concludes a short fulminant illness. We wish to report a case of malignant primary tumor of the heart which was suspected clinically even though it caused unusually mild symptoms at first. Surgical removal of the tumor temporarily restored the health of the patient. Radiation therapy later induced a second remission after intracardiac spread had occurred. Its origin from a cardiac valve sets this tumor apart as an extremely rare cancer only 6 previous cases have been recorded.

Case report

A 21 year-old man an identical twin had sudden severe dyspnea, violent coughing and gross hemoptysis as the first sign of illness, in April, 1960. A chest x-ray film showed only pleural thickening at the left base. His symptoms promptly subsided, but 4 weeks later left pleural effusion was recognized. One month later the initial symptoms recurred. Thoracentesis revealed bloody pleural fluid, and a heart murmur was heard for the first time. The pleural fluid was cytologically negative and no common bacteria, tubercle bacilli, or fungi could be cultured. Bronchoscopy and bronchography were normal. Bilateral scalene node biopsies showed only nonspecific inflammation. During the rest of the summer he stayed active and felt well, except for mild shortness of breath, but the pleural effusion and the heart murmur persisted.

He was admitted to the State University of Iowa Hospitals on Oct. 4 1960. There were no symptoms and his general physical appearance suggested robust health. The blood pressure was 120/60 mm. Hg the pulse was 90 and regular and the rectal temperature was 99°F. The abnormal findings were limited to the chest and confirmed the presence of left pleural effusion. The heart was of normal size but the right ventricle was palpably overactive. The mitral first sound was moderately accentuated and the second sound at the pulmonary area was loud and closely split. Two murmurs were heard at the apex: a Grade 2 low-pitched systolic blow and a Grade 2, medium-pitched diastolic murmur without presystolic accentuation. A second Grade 2, medium-pitched diastolic murmur was present along the left sternal border loudest at the level of the fifth rib. None of the murmurs varied with changes in body position or respiratory phase.

The hemogram urinalysis, and sedimentation rate were normal. Several lupus erythematosus preparations were negative. The chest x-ray film showed straightening of the left cardiac border and left pleural effusion (Fig. 1). Cardiac fluoroscopy after thoracentesis was of no help in outlining specific chamber enlargement or valvular calcification. Review of his earlier x-ray films showed an increase in the Danzer ratio from .43 in April to .47 in October. The T waves of the electrocardiogram were inverted in Leads III and aVF. Cultural and cytologic studies of the bone marrow and the bloody pleural fluid yielded no diagnostic clues. Blood cultures were sterile.

Three possibilities were entertained: rheumatic mitral valvular disease, congenital heart disease with left-to-right shunt, or tumor of the left atrium and pleura. A tumor seemed most likely because of the bloody pleural fluid and the unusual murmurs. The right side of the heart was catheterized to exclude a shunt and to confirm the clinical impression

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Fig. 1. Chest x-ray film taken in October, 1960, showing the left pleural effusion and straightening of the left heart border.

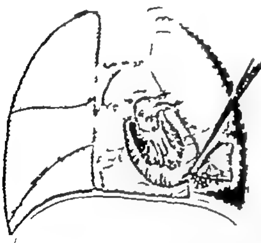


Fig. 2. Drawing to show the location of the tumor and the infarcted segment of the left lower lobe.

of pulmonary hypertension. The mean pulmonary arterial and wedge pressures were elevated at 47 and 35 mm. Hg respectively. No shunt or gradient across the pulmonary valve was found. With this much support for our clinical suspicion, we decided against angiocardiography and determined instead to investigate the pleural disease directly.

On October 27, left thoracotomy was performed and the left lung was decorticated of a thick peel of inflammatory tissue which proved to be organizing blood. The explanation for the hemothorax was found in the inferior pulmonary vein, which was occluded by a firm mass that extended into it from the left atrium. The venous obstruction had infarcted part of the left lower lobe and resulted in collateral varicosities of the pleural surface. One of these had probably ruptured into the pleural space. The captive lung was re-expanded and further investigation of the mass postponed. The patient had an uneventful postoperative course, and on November 17, right thoracotomy and left atriotomy were performed with the pump oxygenator and cardiopulmonary bypass. The left atrium was filled by a polypoid mass which arose from the posterior commissure and the mural leaflet of the mitral valve. The tumor extended retrograde to occlude the inferior pulmonary vein (Fig. 2). The tumor was peeled away from its attachment by blunt dissection and removed from the pulmonary vein by evaginating the vessel. The dissection about the valve was difficult and not all of the tumor could be removed without destroying the leaflets.

The patient made a good recovery. The chest x-ray film cleared completely, and the heart murmur disappeared. The mitral first sound returned to normal, and the pulmonary second sound diminished, although it remained louder than the aortic sound. By December, 1960, he felt well and had begun to resume normal activity at home.

The excised tumor (Fig. 3) was an irregularly ovoid mass 9.5 cm. in greatest dimension. The surface presented thick, finger-like processes and broad nodular excrescences. The tissue was quite firm and resilient, yet pieces of the surface projections broke off easily.

Histologically, much of the tumor consisted of hyalin material and vascular connective tissue with fibrocytes of ordinary appearance (Fig. 4,A). In several areas there were large cells with abundant, pale, faintly basophilic cytoplasm and round or oval nuclei reminiscent of hyperplastic endothelium. Some of these cells were highly pleomorphic and some had abnormal mitotic figures. Some were arranged in linings of clearly recognizable vessels (Fig. 4,B); in other areas they were randomly scattered through the hyalin and connective tissue stroma. In still other areas anaplastic cells merged with relatively mature endothelial cells (Fig. 4,C).



Fig. 3. Tumor excised from the left atrium.





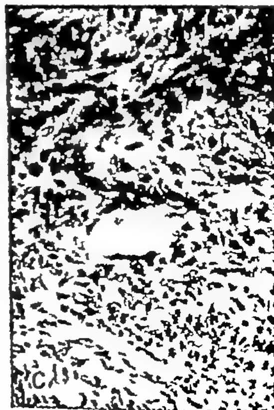


Fig. 4. *A*, Low-power photomicrograph. Most of the tumor is composed of sparsely cellular hyalin connective tissue. *B*, Photomicrograph showing vessel formation by pleomorphic endothelial cells. *C*, Photomicrograph in which some of the cells lining the large vascular space resemble mature endothelium. Adjacent cells are anaplastic and histologically malignant. (*B* and *C* are in opposite column.)

There are no myxomatous or myxosarcomatous areas.

In April, 1961, after 4 months of apparent good health, the patient developed low-grade fever, exertional dyspnea, and intermittent precordial pain. A rapid gain in weight followed, and he complained of a sense of fullness in the right upper quadrant upon exertion. The heart was now enlarged to the anterior axillary line and a loud murmur of tricuspid stenosis was discovered. The loudness of the murmur was strikingly increased during inspiration. A chest x-ray film (Fig. 5) showed an irregular prominence of the left ventricular shadow and marked increase in the size of the heart. Intravenous angiocardiography demonstrated large filling defects in the right atrium and right ventricle, and poor filling of the left ventricle in the region of the cardiac apex. The electrocardiogram showed changes consistent with involvement of the free wall of the left ventricle and the pericardium by the tumor.

He was treated with cobalt-60 radiation, ultimately receiving a tumor dose of 4,388 gamma. This resulted in remarkable improvement in the



Fig. 5 Chest x-r film taken in April 1961 showing ol ien of the ardiac pex by the t mor



Fig. 6 Chest x-r film taken i July 1961 show ng return t normal of the heart shadow after adiation therapy

roentgenog phic ppearance of th heart nd dekmt lthough not complet improvement i the signs of he rt failure The m rmur of tricuspid obstruction remained but decreased in intensity

By July 1961 he till further improved nd w ble t d trenuous exercise w thout dyspne The heart shadow returned to normal (Fig 6). I September dy pnea nd precordial pal t rned The heart shadow w larger tha before and an irregula density was seen for the first time in the base of the left lung The lectrocardiogram showed more pronounced changes. Congesti heart failure returned and clinical evidence of metastases to the pleura nd liver followed H died on Ja 4 1962. Permission for postmortem examination was refused.

The twin brother of the patient was examined n November 1961 H had a short, medium-pitched Grade 1 systolic murmur at the base hich disappeared in the erect position. It was thought t be innocent and of extracardia origin

Discussion

About 170 cases of primary cardiac cancer have been reported and a number of reviews of the subject have already appeared [1-10] but we have found only 6 earlier reports of cancers which began in a cardiac valve [7,11-14]

It is important to exclude the possibility of cardiac metastases from a distant site whenever a malignant tumor of the heart is found Although cardiac metastases usually begin in the right side of the heart they may begin in the left chambers, arriving by way of the pulmonary veins. Metastases to valves however are extremely rare The bilateral thoracotom es and the microscopic examination of the pleura in our patient provided an unusual opportunity to exclude a primary tumor of other chest organs. The histology of the tumor itself suggests that it began in the heart It appears to represent malignant transformation in a hamartoma Previously reported hamartomas of the cardiac valves [7,11] resemble the nonmalignant areas of the tumor in our patient

The prominent clinical features of malignant heart tumors have almost invariably included one or more of the ominous findings of relentlessly progressive heart failure vena caval obstruction pericardial hemorrhage and tamponade serious disturbance of rhythm or gross distortion of the heart shadow on the roentgenograms. Several patients have died suddenly from occlusion of a valve orifice by a pedunculated tumor in the well known manner of atrial myxomas. Metastases or emboli have heralded the onset of trouble in a few patients A striking feature of most cases has been the surprising extent of cardiac involvement before it was obvious on clinical grounds. Thus the eventual course of our patient was expected although dramatic temporary improvement was

achieved by surgery and later with radiation. His early symptoms were remarkably mild a fact which not only made operation feasible but which underscores the importance of early suspicion now that open heart surgery has made the disease theoretically curable.

The occurrence of this tumor in one of identical twins raises the unhappy possibility that one exists or may appear in the other The presence of a murmur in the second twin, although it appears to be innocent has increased our anxiety but it has not been possible to study him further

Summary

The seventh case of a primary sarcoma of a heart valve is recorded. Its presence was suspected clinically despite unusually mild symptoms. Prompt remission followed removal of the tumor and a second remission was later achieved by radiation therapy

W are indebted to George R. Zimmerman, M D Department of Pathology for help in i terpretation of the histologic sections and critical review of the manuscript.

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A myxoma of the pulmonary valve causing severe stenosis in infancy

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Primary cardiac tumors are rare, with an incidence of only 0.05 per cent or less in autopsied material.[1-3] Symptoms apparently due to valvular stenosis or insufficiency are paradoxically associated with cardiac tumors of nonvalvular origin. Those tumors which actually originate from valvular tissue are much less common, are generally asymptomatic, and have never been diagnosed during life.

We have encountered a myxoma arising from the pulmonary valve that produced critical pulmonary stenosis with angiocardiographic findings suggestive of a tumor of the pulmonary valve.

Case report

The patient was a 2-month-old white male baby who was referred to the University of Washington Hospital with cough, poor intake of food, vomiting, and rapid pulse of 5 days' duration. No cyanosis was noted, and the respirations were rapid and shallow. The symptoms gradually increased in severity, and he was referred to the hospital with a diagnosis of congestive failure.

The child was the product of a full-term uncomplicated pregnancy. There was no neonatal difficulty. He was noted to have a heart murmur shortly after birth but was said to have a "normal sized heart" on x-ray examination. There was no history of cyanosis or dyspnea, but the parent thought that his respirations had always been somewhat rapid.

Physical examination. The blood pressure (flush method) was 80 mm. Hg in the right arm and 85 in the right leg; pulse was 160, and respirations were 78 (crying). The patient was a reasonably well-nourished infant, irritable and restless, with occasional nonproductive cough. He was not cyanotic, and there was no apparent edema. Respirations were rapid and shallow. The lungs were clear to auscultation and percussion. The maximal cardiac impulse was at the lower left sternal border. The first sound was of normal intensity; the second sound at the pulmonic area was soft and unsplit. A harsh Grade 3/6 systolic murmur was heard along the left sternal border, loudest at the third intercostal space. An accentuated third sound was heard at the lower left sternal border, followed by a soft, medium-pitched mid-diastolic murmur. The abdomen was soft, and the liver was palpable 1 to 2 cm. below the right costal margin.

The admission hemogram and urinalysis were within normal limits. The electrocardiogram revealed right ventricular overload, right bundle branch block, a wide QRS-T angle, and peaked P over the right precordium (Fig. 1). Cardiac radiograms showed moderate cardiac enlargement, predominantly of the right atrium and right ventricle. The pulmonary vascularity was slightly decreased, and no dilatation of the main pulmonary artery segment was seen (Fig. 2).

The patient was digitalized, with some improvement in heart and respiratory rate, and a moderate diuresis followed. After 3 days the patient underwent cardiac catheterization. All four cardiac ham-

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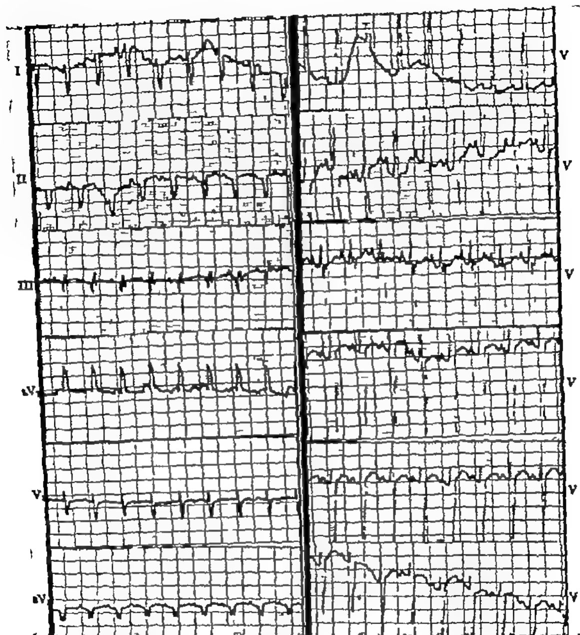


Fig. 1. Twelve-lead electrocardiogram demonstrating right ventricular overload, right bundle branch block, and P pulmonale.

bers were entered, the left side via an atrial communication. A small right-to-left shunt was found at the atrial level. Right ventricular pressure was greater than left ventricular pressure (140 and 115 mm. Hg, respectively). Angiocardiography with injection into the right ventricle, demonstrated severe pulmonary stenosis, with grossly deformed valve (Fig. 3). The patient tolerated the procedure well, but on the following day the cough became more severe with prolonged paroxysms. The child developed cyanosis during these episodes, and was placed in oxygen with mist. Over the next 6 days the infant showed increasing fatigue and listlessness. Because of this deterioration, surgical intervention was elected. In spite of the obvious disadvantage of size and condition, open-heart surgery was performed utilizing cardiopulmonary bypass in deference to the complicated deformity of the pulmonary valve. The patient was placed on bypass with moderate hypothermia. The right ventricular outflow tract was incised and a 10 by 4 by 8 mm. pearly myxomatous mass was found in the area of the pulmonary valve and conus. There was little evidence of normal valvular structures. This



Fig. 2 Posteroanterior and lateral radiograms of the chest, revealing a globular heart and slight diminution of the pulmonary vascular markings.



Fig. 3 Simultaneous posteroanterior and lateral angiocardiograms, after injection of contrast material into the right ventricle. The right ventricle and main pulmonary arteries are filled with contrast material. The arrows point to a filling defect in the region of the pulmonary valve, which was subsequently proved to be a myxoma of the pulmonary valve.

tissue was removed with scissors and punch biopsy instrument and after dilatation a good outflow tract was established. The outflow tract incision was closed, and the patient was taken off bypass after 25 minutes with re-establishment of his circulation in a normal manner.

The infant's temperature was returned to 34°C. before he left the operating room. However during the afternoon he was unable to maintain this temperature which gradually dropped to 32°C. Coincident with this was an inability to maintain an adequate blood pressure. Despite vigorous effort to restore temperature and blood pressure the general decline continued and the patient died approximately 7 hours after returning from the operating room.

On postmortem examination the significant

findings were limited to the heart and lungs. The heart weighed 46 grams (normal 20 to 30 grams) with hypertrophied right ventricular wall that measured 1.0 cm. in thickness, in comparison to 0.5 cm. for the left ventricular wall. The aortic, tricuspid and mitral valves were of normal configuration but were slightly thickened and more opaque than normal. A 2 by 2 by 4 mm. mass of nodular pearly white tissue remained at the site of the operation in the pulmonary valve area, which was unobstructed. The pulmonary artery was unremarkable. The patent foramen ovale measured 1 cm. in diameter. The lungs weighed 110 grams, and beneath the pleura of the right upper, middle and lower lobes were several 0.5 to 0.7 cm. red to purple discolorations.

Microscopically, the surgical specimen had abundant basophilic, myxoid stroma which contained stellate, round, and spindle-shaped nuclei with scant and irregular distribution of connective tissue fibers. The tissue formed several papillary projections of myxoid stroma, most of which demonstrated an apparent cellular lining (Fig. 4,A). In an area with adjacent myocardium the myxoid tissue contained an increased amount of connective tissue close to the myocardial fibers, but there was no invasion or extension of the myxoma into the cardiac muscle (Fig. 4,B). The stroma stained metachromatically with toluidine blue and did not stain with the periodic acid-Schiff reaction.

The aortic, tricuspid and mitral valves were thickened with a diffuse increase of myxoid basophilic stroma between connective tissue fibers, and stellate and spindle-shaped nuclei. There were no papillary projections of myxoid material or tumor formations. Small nodular accumulations of myxoid material were present in two focal areas within the media of the pulmonary artery. There was alveolar congestion of the lungs, with scattered alveoli containing granular edema fluid, and several foci of intra-alveolar hemorrhage. No emboli of fibrin or myxoma were present.

Discussion

Previous descriptions of stenotic pulmonary valves seen at the time of operation or postmortem examination have not included any similar to the tumor found in our case.[11-14] The reports and reviews of cardiac tumors consistently state that tumors which originate on the valves are of no clinical significance.[1-4] The

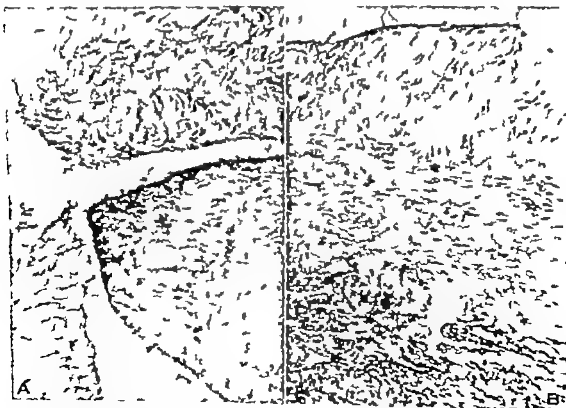


Fig. 4. Myxoma of pulmonary valve, surgical specimen. A, The tumor shows characteristic vacuolated, loose stroma with stellate and spindle-shaped nuclei. The papillary projections are lined, in part, by round and elongated nuclei. B, Increased connective tissue fibers are seen in the myxoid stroma, which does not extend into the myocardial fibers seen in the lower portion of the figure.

only exceptions to this in the literature have been cases of malignant cardiac tumors which have locally grown to a large size in the pulmonary artery [17]

There has been considerable discussion in the literature about the true nature of these cardiac myxomatous masses both mural and valvular The differential diagnoses have included true myxomatous neoplasm organized thrombi and in the case of valvular tumors a form of Lambl s excrescences.[5-8] In the case of cavitary tumors the consensus now seems to be that the majority are true neoplasms whereas the valvular ones may be true neoplasms or rests of primitive endocardial tissue with rare cases of true sarcoma [9,10] We believe that our case is a true neoplasm

Summary

A 2 month-old male infant with severe pulmonary stenosis was found to have a myxoma of the pulmonary valve the diagnosis was suggested by angiocardiography and confirmed by open-heart surgery Previous reports indicate that myxomas of valvular origin are rare and asymptomatic relative to mural myxomas.

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Clinical pathologic conference

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Clinical abstract

History. The patient was a 34-year-old housewife of Japanese origin who was hospitalized for evaluation of chest pain. She had first been told that she had hypertension at the age of 23. At age 29, during hospitalization for therapy of hypertension in Japan, she had had a prolonged episode of chest pain. Findings on serial electrocardiographic studies were said to have been compatible with myocardial infarction. After prolonged hospitalization the patient was discharged and treated with rauwolfia. Although her hypertension persisted, she felt well until 1½ years prior to admission, when she sustained a second attack of severe chest pain. Two and one-half months prior to hospitalization, after coming to this country, the patient had a 30-minute episode of crushing substernal pain with radiation to the left scapula and the inner aspect of the left arm. Since then she had noted increasing fatigue and substernal tightness with exercise. She denied paroxysmal nocturnal dyspnea, orthopnea, and ankle edema.

The past history included a 1-month attack of migratory arthralgia in childhood. A heart murmur had been reported to her. At the ages of 16 and 20 she had had episodes of headache and syncope; lumbar puncture after the second episode was said to have shown blood. There were no focal signs and no neurological residua. She had never been pregnant. The patient's mother had died at age 57 of a "heart attack." The remainder of the history was unremarkable.

Physical examination. At the time of her admission examination she was a thin woman in no distress. The pulse was 100 per minute, and the blood pressures were 184/80 mm. Hg (right arm recumbent), 175/60 (left arm recumbent), 154/60 (right leg recumbent). The optic fundi showed arteriolar narrowing but no hemorrhages or exudates. The heart was enlarged to approximately 2 cm. beyond the left mid-clavicular line. There was sinus tachycardia. The aortic second sound was greater than the pulmonic second sound, and the mitral first sound was loud. A Grade 2 apical systolic murmur was heard, and there was an aortic systolic thrill and a Grade 2 aortic systolic ejection murmur radiating into both carotid regions. A faint blowing diastolic murmur was heard along the left sternal border. The smooth, nontender liver extended 3 cm. below the right costal margin. The pedal pulses were diminished. The remainder of the examination was normal.

Laboratory examination. Urinalysis revealed no abnormalities. White blood cell count (including differential), hemoglobin concentration, hematocrit, platelet count, bleeding and clotting times, and the serological test for syphilis were normal. Fasting blood sugar, serum sodium, potassium, calcium, chloride, carbon-dioxide combining power, and alkaline phosphatase values were within normal limits. Erythrocyte sedimentation rate was 29 mm. per hour; blood urea nitrogen 22 mg. per cent; urea clearance 35 [illegible] per minute (maximum flow); serum cholesterol 270 mg. per cent; serum cholesterol esters 180 mg. per cent; antistreptolysin-O titer 1:100; C-reactive protein 1+; albumin 3.4 Gm. per cent, globulin 3.5 Gm. per cent. A "lupus erythematosus cell" preparation was negative. Circulation time (Decholin) was 14 seconds. A determination of basal metabolic rate was +2. Complete pulmonary function studies were normal. Urinary catecholamines were normal. The stools were negative for ova and parasites.

X-ray examination (Dr. Nels Strandjord). The x-ray films of this patient are indeed interesting. We have an initial frontal chest film taken at the time of admission (Fig. 1). We measure the heart size by comparing the frontal plane area [illegible] square centimeters against predicted area for the patient's height and weight. In this patient, who weighed 100 pounds and was of very small stature, the heart was oversized. We are, of course, measuring area

With the participation of Nels M. Strandjord, M.D., Robert [illegible] Page, M.D., Robert W. Harrison, M.D., Emmet B. Bay, M.D., and N. Samuel Greenberg, M.D. The conference was directed by Robert W. Wissler, M.D., Chairman of the Department of Pathology, University of Chicago Hospitals and Clinics.

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Fig 1 Frontal view of chest demonstrating elongation dilatation and extensive calcification of the aorta

an plaque and not me suring ent lar thickness. More importa however re the findings in the art h The frontal hest film show extensiv alc ification he scending aorta the rch and he descend ng ort h h is elongated nd tor uou Rib not hing is not present nd ould be expected if sev lled reverse coarctation ere present W know tha he blood pressure measured he pa ie arm higher than that in her leg The later l film (Fig 2) show pectus ex t nd agai ery extensiv lcification of the asc nding nd descending aorta Bec se of the degree of the hes deformit the heart is displaced poster iorl Therefore I do not think one is just fied in diagnos ng lef trial enlargement An intra enou py logr m sho ed hat the kidney ere normal pos in size nd ontour Our impression that the ex ensiv alcification in the aorta ery usual f r oman of this age especially one of J panese origi When alcific ion is seen in the scending aorta philis should l ys be considered Although alcification f the scending aorta ma oc ur in patien ith therosclerosi it i rarely bserved in frontal hest film This is because the alcific ion is usually in the medial or inner spect of the scending arch nd is superimposed on the spine Calcific tion if it is seen is more commonly associated th syphilis bec use the resulting tortuosity of the aorta displaces the later l border over the lung parenchyma W must raise the question that this could be philitic aortitis. Certainly the patient has dilatation of the arch elongation of the aorta nd ery extensi calcification, extremely unusu l for her ge nd sex.

Clinical course During the third nd fourth eek of hospitalization she had interm ttent nd unexplained sinu tachy ardia with rates of 110 t 130 per minute Catheterization of the right side of the heart showed normal pressures and oxygen satura tions. Dye-dilution curves were normal. Brachial rterial pressure was 196/65 mm. Hg with heart rate of 136 per mi ute The patient was ad ised to undergo reconstructive aortic surgery but preferred to postpone this. She was discharged on the thirty fifth hospital day on limited acti ity nd nitroglyc erin.

Electrocardiographic examination (Dr. Robert G. Lage). The electrocardiogram (Fig 3) taken on July 9 when the patient was first admitted t the hospital showed depression of the S-T segment in Lead I II III and V_F and elevation of S-T segment in Lead aV I think that this is nonspecific The Q es in the three limb leads are quite mall and not ery helpful diagnostically They are less than 0.04 second in duration and ery shallow The electrocardiogram recorded during the time the patient was having pain (July 23) shows ery marked S-T segment displacement. Chest lead how the change mostly over on the left side of the chest We can see that there ha been a very dra matic change the etiology of which is difficult to determine without knowing the patient' cli ical status nd the drugs the patient wa receiving In November prior to operation, the S-T segments are till depressed. The major change from the first lectrocardiogram is the change in S-T segment nd T wa es hich has occurred n the left precordial lead There is slight notching of the P w the sig ificance of h h is nclear The major hange i the entric lar complex is seen in Lead V V



Fig 2 Left lateral x-ray iew of chest demonstrating pectus exca t m as well as elong tion dilatation and extensi calcific tion of the orta

and V. May I emphasize that in the first tracing prior to pain, prior to the tachycardia, and before the second hospitalization all of the T waves were upright.

Readmission for surgery. Three and one-half months later she was rehospitalized for surgery. During the month prior to her readmission the angina grew worse and responded less satisfactorily to nitroglycerin, orthopnea developed and she had several bouts of nocturnal dyspnea.

Physical examination at the time of readmission was essentially similar to that of the previous admission. Urinalysis, white blood cell count, differential, and hemoglobin were normal. The blood urea nitrogen was 17 mg. per cent, serum sodium was 132 mEq. per liter. She was kept at bed rest, treated with nitroglycerin for frequent anginal attacks, and digitalized without significant diuresis or subjective improvement. On the twelfth hospital day, operation was performed. At the end of an open-heart procedure which lasted 4½ hours her heart would not respond to stimuli, and she was pronounced dead.

Discussion

DR. ADAMS: May I review the pertinent points in the protocol. The patient was a 34-year-old Japanese housewife who knew that she had had hypertension since the age of 23. It is not known how long she might have had hypertension before that. We do not know whether she was ever normotensive. She also had three questionable myocardial infarctions 5 years, 1½ years, and 2 months prior to her admission. The evidence for these is all presumptive. The first incident occurred during treatment of her hypertension in a hospital. Of course, various ischemic episodes are common as a result of the treatment of hypertension, but I do not see that this helps us to tell whether her initial attack was an infarction or something else. From the time of the last episode, that is, for 2 months, she had suffered from angina. The presence of arthralgias in childhood supports a diagnosis of rheumatic disease. She had had two unusual episodes at the ages of 16 and 20; blood was found in the spinal fluid after the second. Perhaps the spinal fluid was not analyzed after the first episode. This is certainly suggestive of subarachnoid hemorrhage. Her mother died at the unusually early age of 37 and of a heart attack.

The physical examination revealed systolic hypertension with the blood pressure slightly lower in the left arm than in the right and still lower in the legs. Only one

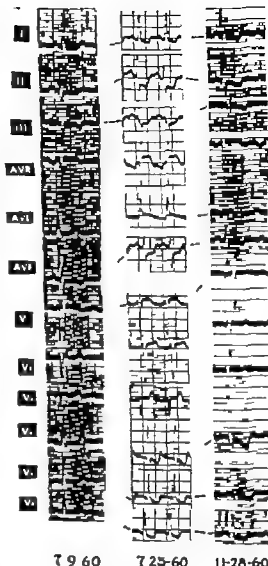


Fig. 3. Electrocardiograms. On July 9, 1960, the pulse rate is 92 per minute, P R is 0.16 sec., and QRS is 0.08 sec. On July 23, 1960, the pulse rate is 130 per minute, P R is 0.15 sec., and QRS = 0.09 sec. On Nov. 28, 1960, the pulse rate is 94 per minute, P R is 0.16 sec., and QRS is 0.08 sec.

leg is mentioned, but the pedal pulses were weak bilaterally. The fundi are suggestive of true hypertension in that the arterioles are narrow, and perhaps the diastolic pressures would be higher if it were not for lesions in the heart. The apical murmur is not helpful in diagnosis. The basal murmurs and the thrill are those of aortic stenosis and insufficiency. The aortic second sound is definitely present, which means that the aortic valve, if stenotic,

must have a narrow annulus. Calcified valves and I believe markedly fibrotic valves usually do not produce a second heart sound even in the presence of hyper tension. Certainly the wide pulse pressure indicates that the aortic insufficiency was the predominant lesion from a dynamic standpoint. The liver is enlarged and sug gests heart failure although according to the protocol it occurred earlier than any other manifestation of heart failure At the time of the first observation there was a mild elevation of the blood urea nitrogen and diminution of the urea clearance but later the blood urea nitrogen returned to 17 mg per cent, an approximately normal figure I consider the C reactive protein of 1+ to be equivocal. The mild elevation of the serum globulin could be the result of heart failure or could be associated with a number of diseases. I am somewhat pre occupied by the intermittent tachycardia which was present throughout her illness here It should be noted that toward the end she had more symptoms of failure to go along with her respiratory symptoms and enlargement of the liver The angina became worse and notching of the P waves of the electrocardiogram was present. She was operated upon and died at the time of operation It is interesting that we have not been told what operation was per formed and this is not immediately obvious to me

I think that the first diagnosis to be con sidered is essential hypertension with an accelerated atherosclerotic process in a young woman with myocardial infarction angina and heart failure even though this would be unusual. The low blood pressure in the legs might be explained by a local arterial lesion This diagnosis is indirectly supported by the death of the mother from a heart attack at the age of 37 We must, however account for the valvular lesions which seem quite definite, and also for the subarachnoid hemorrhages if this is indeed what these incidents were.

Syphilitic aortitis would account for the aortic valve lesion could have caused the ischemic episodes whether they were in farctions or not and could produce an increased tendency for aortic calcification The heart failure could also be attributed to this. The nonreactive serology does not prove that syphilitic aortitis is not present but is of course a point against it. This diagnosis does not help us to account for the subarachnoid hemorrhages. Although indi viduals with syphilitic heart disease may have tertiary syphilis in the nervous sys tem the usual manifestations do not re semble the symptoms of this patient The lower blood pressure in the legs would be unusual for syphilis. Syphilitic aortitis is usually most marked in the thoracic aorta, and the lesions tend to be less severe in the abdominal aorta. One would not expect obstruction in the lower aorta.

I must mention rheumatic heart disease which I cannot rule out but must discard because it does not account for the entire clinical picture

I must consider polyarteritis nodosa which may involve the coronary arteries and could account for the cerebral symp toms. This would be compatible with the presence of C reactive protein the rapid erythrocyte sedimentation rate and the elevation of the serum globulin The fact that eosinophilia was not present need not alarm us for eosinophilia may be inter mittent in polyarteritis nodosa and normal eosinophil counts are not uncommon One other point that would fit neatly into this picture is the intermittent tachycardia The low-grade inflammatory process of poly arteritis nodosa may produce acceleration of the heart rate beyond that which the degree of fever would justify Polyarteritis nodosa could also account for the mild diminution in renal function However this mild diminution in renal function could occur as a result of heart failure Polyarteritis nodosa would not account for the changes in the aortic valve. I have found no report of calcification of the aorta in polyarteritis nodosa and the calci fication of the aorta must be accounted for

Takayasu's disease or pulseless dis ease should be considered It would be an exaggeration to say that this patient was pulseless, but her blood pressure was differ ent in different extremities and one is attracted to this diagnosis because more cases of this disease have been reported in Japan than in the rest of the world com bined This woman lived in Japan until fairly recently Takayasu's syndrome is also common in young women and is

characterized by obstruction of branches of the aortic arch and this occasionally includes the coronary arteries and therefore could give rise to the ischemic episodes and could account for the lower pressure in the left arm. Against this diagnosis is the lower pressure in the legs, for predominant involvement of the lower legs is very uncommon. Trophic changes in the areas of the vessels of the upper extremities and the head may also be present, but of course one would not expect to find such changes with the pulses present. This diagnosis does not account for the valve lesions, and neither does it account for the calcification in the aorta. The lesions in Takayasu's syndrome are quite variable and it is doubtful that it is either a clinical or pathologic entity. All of the descriptions that I have been able to find speak of inflammatory and fibrotic changes and not of calcification.

The final diagnosis to be considered is coarctation of the aorta. This could account for arteriosclerosis and calcification of the aorta. It could account for the low blood pressure in the legs. This disease is frequently associated with microaneurysms in the brain and subarachnoid hemorrhage. It is also frequently associated with a bicuspid aortic valve and aortic insufficiency and subaortic stenosis is rather frequently found in association with coarctation. Against this diagnosis is the fact that it is more common in males than in females by a ratio of 4 or 5 to 1. Usually it is not associated with coronary artery disease. However coarctation of the aorta may be associated with dissecting aneurysm of the aorta and dissecting aneurysms could have produced the angina. It would be uncommon for a person to recover from three dissecting aneurysms but this is possible. If coarctation is present, an associated patent ductus arteriosus, which is common, might mimic the findings of aortic stenosis and insufficiency. The murmurs in this patient seem to make patent ductus unlikely and I also am inclined to reject the diagnosis of patent ductus because of the fact that findings obtained by catheterization of the left side of the heart were normal. Patent ductus is not compatible with the normal pulmonary arterial oxygen saturation and pressure.

The aorta appears to be continuous on the x-ray examination. Ordinarily in coarctation the knob is not quite that prominent while there may be poststenotic dilatation of the aorta beyond the coarctation. Still I would favor coarctation of the aorta as the most probable diagnosis. An unusual form of Takayasu's syndrome would be my second choice.

DR. RAY: I wonder whether calcification of the aorta occurs in Marfan's syndrome or some variant of it. The family history of the mother dying at a fairly early age of some sort of heart attack suggests this possibility.

DR. STRANDJORD: If this patient had had the clinical characteristics of Marfan's syndrome, it certainly would fit.

Several cases of cystic medial necrosis of the aorta apparently identical to that of Marfan's syndrome have occurred in the absence of any other stigmata of Marfan's syndrome. In half a dozen descriptions of the pathologic findings in this disease, however, I found no suggestion that calcification of the aorta occurred.

DR. ADAMS: I also studied a number of reports of cystic medial necrosis of the aorta and could find no description, clinical or pathologic, of arterial calcification.

DR. ANGEVINE: At autopsy the body of this thin Japanese woman weighed 98 pounds and was 63 inches long. There was a 24.0-cm. intact recent mid-sternal incision and a second short 3.0-cm. incision in the right hemithorax. The left pleural space contained 200 ml. of clotted blood. The heart weighed 500 grams and the left ventricular wall was 1.0 to 2.5 cm. thick. Diffuse subepicardial hemorrhage was present, and a Teflon graft, 4.0 cm. long, had been inserted into the ascending aorta to replace a resected segment. A flannel patch had been sutured into the aortic ring to reinforce the graft externally. There was thickening of the aortic cusps, and the valve appeared to be insufficient. A flannel patch had been sewn into the posterior aortic cusp in an attempt to repair the posterior valve cusp which had apparently split during operation. The circumference of the valve after the operation was 7.0 cm., which would be within normal limits. There was no specific gross or microscopic valve lesion. The proximal



Fig 4 Aorta opened lengthwise shows severe diffuse atherosclerosis The carotid innominate and subclavian arteries are severely diseased. The Teflon graft is intact

end of the Teflon graft appeared to produce partial occlusion of the right coronary ostium There was extensive calcific atherosclerosis of the entire aorta including the aortic arch and extending into the coronary innominate carotid subclavian and renal arteries (Fig 4) Severe atherosclerosis also extended into the mesenteric and iliac arteries. There was moderate atherosclerosis of the major cerebral vessels but no anatomic evidence of brain damage. The kidneys weighed 100 and 130 grams right and left respectively The renal capsules were stripped with ease there were no gross abnormalities of the kidneys despite the severe arterial lesions. Microscopically the heart showed fibrosis which replaced myocardial fibers in the ventricular septum and anterior wall of the left ventricle (Fig 5) compatible with an old anteroseptal myocardial infarction. There was also individual myocardial fiber hypertrophy but no evidence of acute infarction or rheumatic stigmata was present. Microscopically the aorta showed extensive medial degeneration (Fig 6) with fibrosis and overlying atherosclerotic plaques which contained abundant cholesterol clefts. Similar changes were present throughout the aorta and extended into the carotid innominate subclavian iliac mesenteric and renal arteries. Aldehyde fuchsin trichrome stains for elastic tissue (Gömöri) showed extensive disruption of elastic fibers present at all levels of the aorta with medial degeneration between them No microscopic evidence of syphilitic aortitis was present Both internal carotid arteries were almost completely occluded by atheromatous plaques and a recent thrombus was found overlying a plaque in the right internal carotid artery

There were varying degrees of muscular hyperplasia and focal thickening of the arcuate arteries of the kidney Very little evidence of scarring was present, although there was focal hyalinization of glomeruli Similar changes were present in the small vessels of the pancreas and in the periadrenal fat. Additional organs are of particular interest because of their possible relationship to atherosclerosis or to disturbances in lipid and cholesterol metabolism In the ovaries, follicles in all stages of development and a large recent corpus luteum were seen. The breast tissue appeared to be normal for a premenopausal woman except for mild chronic periductal inflammation The thyroid gland was histologically normal The parathyroids were normal

Despite the severe atherosclerosis in this young Japanese woman we believe that the primary disease was probably medial degeneration with superimposed severe atherosclerosis. The conditions in which medial degeneration occur have been mentioned by Dr Adams. Marfan's syndrome is probably the most common Occasional instances have been reported in pregnancy and also in association with congenital cardiovascular anomalies. Factors which have been considered in the pathogenesis of medial degeneration are syphilis, obliterative changes in the vasa vasora, endocrine disturbances, such as

hyperadrenocorticism and severe infections, and intoxications. The role of diet has been studied experimentally. Medial degeneration can be produced by the feeding of *Lathyrus odoratus*[8] or by means of hypervitaminosis D.[9]

The factors which contribute to the superimposition of the atherosclerosis can only be speculative. As Dr. Adams mentioned, in large series of autopsies of patients with Marfan's disease there has been very little correlation with severe atherosclerosis or calcification of the aorta. The role of hypertension has not been fully studied although in the presence of medial necrosis, hypertension is thought to be a predisposing factor in the development of dissecting aneurysm of the aorta.

Although this patient does not fit into the category of "pulseless disease," she seems to fit into the category of the "aortic arch syndrome," which may be produced by occlusion at or near the aortic arch by syphilitic aortitis with or without aneurysm, trauma with or without aneurysm, nonspecific arteritis, and superior mediastinal tumors. None of these appear to have been present.

Autopsy diagnoses: Severe medial degeneration and superimposed severe atherosclerosis of the entire aorta; aneurysmal dilatation of the ascending aorta with recent resection of the aneurysm with replacement by Teflon graft and felt padding; sclerosis and insufficiency of the aortic valve; severe atherosclerosis of coronary, innominate, carotid, subclavian, renal, iliac, and mesenteric arteries; myocardial scars of past myocardial infarction. Chronic cervicitis, erythroid hyperplasia of the bone marrow, and acute hyperemia of the liver.

DR. GLAGOV: I would like to emphasize that this is no ordinary atherosclerosis from the point of view of localization of lesions. The distribution of atherosclerosis in the arterial tree of this patient departs from that which is usually seen at autopsy. It is well known that certain segments of the arterial tree are less frequently involved by atherosclerosis than others. This is well shown if one compares different arteries of the arterial tree in a single individual. In patients with severe aortic atherosclerosis, involvement of the main renal arteries by atherosclerosis is unusual. In a series of 200 consecutive autopsies at the University of Chicago only 16 showed any gross involvement of the renal arteries, and these were always less involved than was the corresponding aorta. The coronary arteries, however, were less involved, equally involved, or more involved than were the corresponding aortas. These are not merely differences in the rate of development of atherosclerosis in the segments mentioned; for a given degree of aortic atherosclerosis is associated with a range of grades of both coronary and renal artery atherosclerosis, even though the involvement of the renal arteries is always much less than that of the corresponding aorta. The arterial tree of the patient whose case we have discussed today departs markedly from the usual pattern of distribution of atherosclerosis in that there is uniformly severe involvement throughout.

DR. WISSLER: We are faced with the problem of a young woman with very severe arteriosclerosis who should have had maximal protection against this disease because of youth, femininity, and her Oriental background. She has, as far as we know from the evidence at hand, none of the contributing metabolic derangements which might be expected to counteract her natural protection, such as nephrosis, hypothyroidism, diabetes, or essential cholesterolosis. Even so, her blood cholesterol is somewhat high, not only for a young female in Japan but probably for most of the population in this country. She does have a history of long-standing hypertension, and she does have evidence of considerable medial disease of the large arteries. There is no evidence of syphilis. Where does this leave us? From our own studies, we believe that there are three major factors that are often interrelated in the development of atheromatous disease. Most Americans develop atherosclerosis rather slowly, probably mainly as a result of a moderate excess in diet. In other instances disturbed lipid metabolism of the types mentioned may be added to dietary excess. Arterial injuries are also important under some circumstances. Syphilis is certainly one of these. I think that this patient had severe arterial injury in addition to some moderate derange-

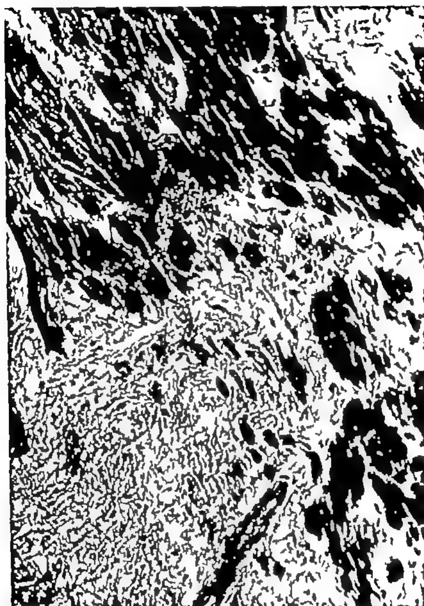


Fig. 5. Microscopic view of the anterior wall of left ventricle. The extensive myocardial fibrosis is probably the result of a healed myocardial infarct (×160).

ment of lipid metabolism which we do not really understand.

What is it that causes the rapid progression from a fatty plaque to a complicated lesion in this instance at an accelerated rate? We have experimental evidence that the accumulation of blood lipids in the arterial wall is accompanied by reaction of the arterial cells to the irritating lipids. Sometimes there appears to be decreased catabolism of abnormal lipids in the arterial tissues as a major factor in the progression of the disease. This is borne out by studies which we have been carrying on in subhuman primates. In this patient a defect in the metabolism of the arterial wall and the hemodynamic stress of hypertension are probably the most important factors.

Dr. Angevine has listed some of the factors which have to be considered when we try to understand why the media of large vessels might be severely damaged. This subject of medial injury was thoroughly reviewed by Hueper[4] about 20 years ago and we can add little more now. I think that at least three endogenous injurious sub-

stances must be considered though we have very little evidence for them in this case.

One is certainly histamine, which can be shown to produce severe medial degeneration in experimental animals.

Epinephrine will certainly produce medial lesions. Lesions similar to those of this patient have been noted in a few patients with pheochromocytoma or in animals after prolonged treatment with epinephrine. Our recent experiments with primates have indicated a great acceleration of the atheromatous component of arterial disease when ephedrine has been given intermittently along with an atherogenic ration.

Finally parathormone has to be mentioned. Although the parathyroid glands were apparently normal in this case there is very well-documented evidence that excessive parathormone can produce this kind of very severe degenerative change in the media of arteries.



Fig 6 Microscopic view of the thoracic aorta. Very thick atheromatous change (P) with cholesterol clefts is present. The media (M) shows muscle degeneration and disruption and degeneration of the elastic fibers. The adventitia (A) is markedly thickened and fibrous. The aorta was essentially similar throughout (×100).

Exogenous toxins such as nitrites and nitrates, have been implicated in medial arterial injury both experimentally and clinically as have arsenic manganese and mercury but we have no hint of these toxic substances in this case Lathyrism which was mentioned is also a potential mechanism for injury of the media of arteries, but so far its connection with human disease is not apparent We are thus left with the unanswered questions What metabolic mechanism injured the arteries of this individual How was this connected with the very rapid progressive development of atheromatous disease

Some of the pathologic changes in the aortic valve and the first portion of the aorta were obliterated by the surgical intervention I think that it might be useful to know what this valve looked like at the time of operation Could Dr Harrison comment on the case and tell us what he found and what he thinks the essential lesion of the aortic valve was before the flannel patch was inserted?

DR HARRISON We were certainly impressed by the extensive atherosclerotic process when we attempted to cannulate this patient s right common femoral artery a procedure which is preliminary to instituting our heart lung bypass. We were unable to cannulate the right common femoral artery because of the extensive atherosclerotic process but were eventually able to cannulate the left At the time of operation we found that the ascending aorta was markedly dilated and somewhat tortuous. After placing a clamp on the ascending aorta just proximal to the innominate artery we opened the ascending aorta and visualized the valve. The annulus of the aortic valve was dilated but the aortic cusps appeared to be relatively normal except for some thickening However they did not appose and we attributed this to a dilatation of the aortic annulus We thought that since the valve leaflet substance was not severely damaged we could reduce the circumference of the aortic annulus and thus allow the leaflets to coapt. We attempted to enhance this effect by suturing in the region of the commissures. We also considered it necessary to replace the ascending aorta because it was aneurysmal and the wall markedly thinned This procedure prolonged the operating time. During this time the circulation to the myocardium was impaired I might add that when we opened the ascending aorta we found the left coronary ostium completely occluded by an atheromatous plaque and the right coronary ostium partially occluded by an atheromatous plaque We removed these plaques in hopes that myocardial blood flow would be improved We were hoping to protect the myocardium by means of hypothermia during the procedure We reduced the myocardial temperature to between 5 and 10°C by packing the heart in frozen saline solution thus reducing the metabolic demand of the heart However after 3 hours of this the heart could not be resuscitated When it was warmed it continued to fibrillate In view of the previous myocardial damage that this patient had suffered the additional insult of the surgical intervention could not be tolerated

DR GREENBERG We have been searching the hospital records in an attempt to study the incidence of myocardial infarcts in healthy young females between the ages of 15 and 40 with normal menses Our search is almost complete and of a dozen clinical infarctions three have been confirmed at autopsy There was one diabetic patient, one patient with hypercholesterolemia and one patient with emboli from subacute bacterial endocarditis. The rest were hypertensive. I would like to emphasize that the prolonged hypertension for at least 11 years may have played an important role in counteracting the beneficial effects of ovarian hormone.

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Fundamentals of clinical cardiology

Therapeutic modalities in the management of cerebral vascular insufficiency

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The individual prognosis of untreated cases of acute cerebral vascular insufficiency is extremely variable and in consequence the efficacy of any therapeutic modality in this disorder is difficult to evaluate. It may be significant that approximately similar remission rates have been claimed for such diverse methods of treatment as administration of vasodilator drugs, anticoagulant therapy, and vascular surgical intervention.

The various physiologic factors which make the natural course of cerebral vascular insufficiency difficult to predict include (1) the uncertain hemodynamic effectiveness of inconstant anatomic connections between internal carotid and vertebral arterial systems and of other significant collateral sources of cerebral blood supply, and (2) variable efficiency of the several homeostatic mechanisms (e.g., cerebral vasodilation, reflex changes in blood pressure) which tend to preserve stability of cerebral oxygen delivery. In addition, taxonomic obstacles in the evaluation of therapeutic experiences are represented by a lack of standardized classification of the neurological types of cerebral vascular insufficiency (see Table I for such a previously proposed classification[7]) as well as by variability in patient material which may consist largely of acute cases in one series and chronic cases in another. Finally, it must be borne in mind that the genesis of intermittent cerebral ischemia may have various or even multiple origins (Table II), as a result of which clinical change for better or worse may be completely unrelated to the type of therapy instituted. In spite of the manifest difficulties in evaluating the role of physiologic variables in the outcome of cerebral vascular insufficiency, critical examination of current medical and surgical approaches to this disorder is warranted because of their wide employment. It must be admitted that present opinions, based as they are upon comparatively poorly controlled clinical experience, should be regarded as tentative.

It can hardly be denied that any basic therapeutic approach to the problem must, in view of the underlying pathophysiology, depend upon either a reduction of cerebral oxygen requirement or an increase in cerebral tissue oxygenation. In regard to the former, although animal experiments[4] have demonstrated that hypothermia may afford considerable protection against ischemic cerebral infarction by reducing

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Table I. Clinical classification of cerebral vascular insufficiency

TI	*Transitory ischemia*—acute neurological dysfunction with recovery to pre-episodic state
TSR	*Transitory ischemia with stable residua*—brief neurological dysfunction with persistence of minor subjective or objective neurological deficits
TPD	*Transitory ischemia with progressive deterioration*—increasing disability after each repeated episode of acute cerebral dysfunction
DCD	*Diffuse ischemic cerebral deterioration*—progressive intellectual impairment or behavioral disturbance
IPI	*Infarct with progressive improvement*—acute severe neurological deficits with appreciable continuing recovery
ISR	*Infarct with stable residua*—severe ischemic cerebral dysfunction with some subsequent return of function but with persisting neurological deficits
IPD	*Infarct with progressive deterioration*—increasing neurological dysfunction after severe ischemic episode
ICU	*Ischemia course undetermined*—early observation or medical or surgical intervention immediately after ischemic insult rendering a treated prognosis difficult

cerebral metabolic requirements, clinical application of this important principle has not yet been given significant consideration. Although much more attention has been given to exploration of the second major principle, the direct approach (that pure oxygen under increased pressure may permit a considerable increase in diffusion of this gas into ischemic brain tissue[10]) has as yet yielded insufficient evidence upon which to base even provisional judgment. The bulk of clinical attention in the management of cerebral vascular insufficiency is directed to the improvement of the cerebral circulation. Efforts commonly are made to arrest the progress of cerebral vascular degeneration by the prescription of diets restricted in fat or cholesterol content or by the administration of certain agents which may influence lipid metabolism. Although such therapeutic aims may have psychological value and restricted diet may incidentally improve obesity, there is reason to doubt that such efforts can appreciably influence established cerebral vascular disease in man.

The hope is widely entertained that employment of vasodilating drugs may so reduce cerebral vascular resistance that a therapeutically effective increase in cerebral blood flow will result. Unfortunately, critical examination of the effects of the vasodilator drugs indicates that any reduction of cerebral vascular tonus which results from their use is more often than not associated with an at least equivalent fall in systemic blood pressure, so that the over-all cerebral blood flow remains unimproved and may even be reduced.[11] Nevertheless, it has been claimed that the vessels to ischemic cerebral areas may be particularly sensitive to the action of such agents or that the drugs may favorably influence flow through collateral channels. These hypotheses, unsupported by quantitative data, seem to be highly conjectural in view of the demonstration by others that an apparently maximal local vasodilatation occurs in response to accumulated end products of metabolism and to the change in pressure gradients which accompanies cerebral vascular occlusion.[12,13] Table III reviews cerebral hemodynamic data obtained during the administration of commonly available general vasodilators. Two newer drugs of this type (Cyclospasmol[1] and Vasodilan[14]) are claimed to be clinically effective, but this appraisal must be viewed with reservation pending the acquisition of quantitative information concerning their cerebral circulatory effects.

The inhalation of carbon dioxide and intravenous carbonic-anhydrase inhibitors constitute exceptions to the observation that most vasodilator drugs do not induce a quantitatively demonstrable increase in cerebral blood flow.[15] Nevertheless, even these agents are not invariably effective in patients with cerebral vascular insufficiency,[1] and their therapeutic value has not as yet been unequivocally proven. In any event, they are practical only for emergency employment during attacks of acute cerebral ischemia.

There can be no question but that the reduction of blood pressure may often contribute to the genesis of intermittent

cerebral ischemia.[8,9] Therefore it is mandatory in all cases of cerebral vascular insufficiency to attempt to correct or obviate systemic circulatory disorders responsible for hypotensive episodes. (It is of corollary importance to exercise caution in the treatment of hypertensive vascular disease in these patients since precipitous reduction of blood pressure to even normotensive levels may induce cerebral ischemic episodes because of failure of cerebral vascular tonus to decrease proportionately.[7]) In many instances, prophylactic administration of vasopressor agents to stabilize the blood pressure may be physiologically justified although in the normotensive individual a moderate increase in blood pressure as can be achieved by administration of sympathomimetic amines, is usually not accompanied by an increase in

Table II. Genesis of cerebral vascular insufficiency

I. Intracranial factors
- A. Degenerative vascular disease
- B. Thromboembolic vascular occlusion
- C. Intracerebral vasospasm
  1. Hypertensive encephalopathy
  2. Traumatic dissecting aneurysm

II. Aortocranial hemodynamic abnormalities
- A. Degenerative vascular disease
  1. Stenosis
  2. Elongation and kinking
  3. Thrombosis
  4. Brachiocephalic insufficiency
  5. Traumatic spasm or dissecting aneurysm
- B. Compression by cervical osteophytes

III. Systemic circulatory disorders
- A. Cardiogenic hypotension
  1. Decreased venous return
  2. Paroxysmal arrhythmias
  3. Myocardial insufficiency
  4. Valvular heart disease
- B. Peripheral hypotension
  1. Carotid sinus or aortic arch reflex sensitivity
  2. Drug-induced vasodilatation
  3. Hypovolemia
- C. Increased viscosity of blood
  1. Polycythemia, sicklemia, macroglobulinemia
  2. Lipemia (?)

cerebral blood flow since a parallel increase in cerebral vascular resistance occurs because of reflex vasoconstriction. There probably is little basis for concern that these agents may contribute to cerebral vascular spasm inasmuch as it may more reasonably be suggested that, as previously stated on experimental[9] as well as teleological grounds, the cerebral vessels which supply a marginally oxygenated area of the brain tend to be maximally dilated or otherwise relatively unresponsive to any vasoconstrictor influences.

Cerebral vascular resistance is sometimes abnormally increased by an elevated viscosity of the blood as in polycythemia, sicklemia, and macroglobulinemia. It is well known that patients with these disorders are subject both to intermittent cerebral ischemia and to cerebral infarction. Unfortunately at present, only in polycythemia can specific treatment be instituted with, among other goals, reduction of the incidence of cerebral ischemic episodes. Even in the absence of these diseases lipemia has been claimed to increase the viscosity of the blood sufficiently so that a significant reduction of flow might occur in the smaller cerebral vessels.[20] Both dietary restriction and the administration of lipid mobilizers have been advocated on this basis, without, as in the case of so many other modalities, clinical evidence to suggest a definite effect.

Still another commonly employed therapeutic modality in cerebral vascular insufficiency is the administration of anticoagulant drugs in the hope of obviating thrombotic occlusion or of delaying it until collateral sources of blood supply have been able to develop. Although our experience[21] and that of others[22] suggest that long-term anticoagulant therapy in cerebral infarction with stable residua is of dubious value, the administration of these agents appears to be warranted in transient cerebral ischemic attacks with or without minimal stable residua, and even in cerebral infarction early in the disorder when its course and etiology are as yet undetermined, i.e., until there is stabilization of the neurological disturbance, obvious progressive deterioration, or identification of aortocranial occlusion. It has been postulated that clinical improvement of intermittent

Table III. Vasodilators and cerebral hemodynamics

Drug	CBF		CVR		MAP		Reference
	C	E	C	E	C	E	
Nicotinic acid	54.0	57.0	2.3	2.1	114	109	Scheinberg, P.: Circulation 1:1148, 1950
Papaverine hydrochloride	56.6	63.9	1.7	1.4	98	85	Jayne, H. W., Scheinberg, P., Rich, M., and Belle, M. S.: J. Clin. Invest. 31:111, 1952
Tolazoline hydrochloride (Priscoline)	57.0	52.0	1.6	1.7	93	88	Scheinberg, P., Blackburn, I., and Rich, M.: J. Clin. Invest. 32:125, 1953
Histamine	41.9	44.5	2.8	2.1	102	89	Alman, R. W., Rosenberg, M., and Fazekas, J. F.: A.M.A. Arch. Neurol. & Psychiat. 67:354, 1952

CBF indicates cerebral blood flow in milliliters per 100 Gm. of brain per minute. *CVR* indicates cerebral vascular resistance in millimeters of mercury per milliliter per 100 Gm. of brain per minute. *MAP* indicates mean arterial blood pressure in millimeters of mercury. C, Control. E, Experimental.

cerebral vascular insufficiency in response to anticoagulants as described by some workers may be based upon prevention of intravascular labile fibrin aggregates which have been thought to be sometimes responsible for transitory cerebral ischemia.[30] It seems equally probable that the natural course of the disease with particular reference to intermittent vertebral basilar insufficiency may more or less often be in the direction of improvement as has been frequently observed in symptomatically and supportively treated acute cases of minor to moderate severity.

The aim of surgical correction of functionally impaired aortocranial vessels is restoration of flow to enhance cerebral oxygen delivery. This may be curtailed because of congenital variations in the caliber of aortocranial vessels or because of the frequent anatomic asymmetry of the circle of Willis. The percentage of flow carried via the carotid system has been estimated to range from 97 to 62 per cent,[31] whereas that of the vertebral basilar system varies from 38 to 3 per cent. (How much of this variability is due to vascular disease was not specified.) It is apparent that cerebral regions which receive only marginally adequate rates of blood flow (because of anatomic anomalies) would be particularly vulnerable to further even slight reduction of flow whether due to systemic circulatory disturbances or to degenerative disease of aortocranial or intracranial vessels. The development of collateral sources of blood supply in such instances as well as of other homeostatic mechanisms would, however, tend to compensate for the anatomic deficiencies. The impressive potential for spontaneous compensation of even severe restriction of blood flow through aortocranial vessels may be adjudged from the observation that patients can be asymptomatic and have essentially normal quantitative hemodynamic measurements in spite of bilateral complete occlusion of the internal carotid arteries.[32] It is evident from the variable clinical course of cerebral vascular insufficiency that not all patients with aortocranial disease are able to develop compensatory hemodynamic mechanisms and in these cases, angioplasty would appear

Table IV. Indications for aortocranial angioplasty

1. Evidence of intermittent cerebral vascular insufficiency from compression or kinking of vertebral or carotid arteries
2. Brachiocephalic insufficiency ("subclavian steal")
3. Poor response to anticoagulant therapy
4. Acute cerebral infarction with progressive deterioration

to be indicated. Special indications for panangiography with a view toward immediate surgical intervention without attempting a trial of anticoagulant therapy are indicated in Categories 1 and 2 of Table IV. A history of recurrent cerebral vascular insufficiency consistently precipitated by turning or extension of the neck or by exercise of an upper extremity suggests intermittent compression of a vertebral or carotid artery or stenosis of the subclavian artery proximal to the origin of the vertebral artery.[36,37] The latter condition should also be suspected when there is a significant difference in arterial pressure between the two arms or when a bruit is present over the subclavian artery.[38] Not infrequently patients may continue to experience recurrent cerebral ischemic episodes despite well-controlled anticoagulant therapy. Under such circumstances cerebral panangiography appears to be warranted with the hope of demonstrating and correcting a surgically accessible lesion. Such studies must be interpreted with great care since on occasion a second angiographically unimpressive or even unrecognized aortocranial lesion may be primarily responsible for the cerebral ischemic attacks. For example in patients with signs and symptoms characteristic of vertebral-basilar insufficiency and with demonstrable vertebral-basilar artery disease correction of stenosis of the vertebral artery may yield clinically disappointing results whereas correction of concomitant stenosis of the internal carotid artery, if present, may sometimes more satisfactorily improve posterior cerebral circulation by way of patent communicating arteries. Finally those cases of acute cerebral infarction with progressive deterioration in which disease of a carotid artery can be demonstrated (not necessarily contralateral to the neurological deficits) also constitute an indication for immediate efforts to restore flow through the stenotic or occluded vessel.

From the hemodynamic standpoint, the therapeutic effectiveness of a technically successful angioplasty should be predictable on the basis of measurements of intra-arterial pressure before restoration of flow is attempted. Where the pressure above an angiographically demonstrated stenotic lesion is found not to be materially reduced the implication is that the circle of Willis or other collaterals are functioning satisfactorily and that the lesion is not of primary pathophysiologic significance. On the other hand where the intra-arterial pressure cephalad to the lesion is markedly reduced then successful angioplasty may be expected actually to improve the cerebral blood supply although the clinical effectiveness of the procedure may depend upon the presence and severity of yet other hemodynamic abnormalities.

Summary and conclusions

Critical examination of the available armamentarium for management of cerebral vascular insufficiency suggests that assessment of its value is rendered difficult by our inability to quantitate either the hemodynamic effectiveness of spontaneous homeostatic mechanisms or the functional capacity of the circle of Willis. In addition the multiple genesis of many cases of intermittent transitory cerebral ischemia also complicates evaluation of one or another form of therapy. Nevertheless there presently appears to be at least theoretical justification for the employment of certain cerebral vasodilators, systemic vasopressor agents and anticoagulants in the medical management of cerebral vascular insufficiency. Where stenotic or occlusive lesions of accessible portions of aortocranial vessels may be demonstrable surgical restoration of flow in these vessels may be beneficial in some cases. A more precise and reliably objective means is required for evaluation and comparison of the clinical courses of patients with cerebral vascular insufficiency untreated and treated by various medical and surgical procedures.

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Evaluation of preanesthetic medication in cardiac patients

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Dosage and timing of preanesthetic medications must be carefully evaluated for each individual cardiac patient about to be subjected to surgery so that a particularly desired response is achieved without deleterious effect.

Appropriate medication before a local, regional, conduction, or general anesthetic may facilitate and make safer the conduct of anesthesia. However, with present-day anesthetic agents and techniques, preanesthetic medication is rarely absolutely necessary. When in doubt, the physician would be most wise to omit preanesthetic drugs completely. If the anesthesiologist then thinks that one or another effect should be established before anesthetic agents are administered, a drug may be given intravenously, which will usually result in maximal effect in 5 to 10 minutes.

Atropine and scopolamine. The belladonna derivatives, atropine sulfate and scopolamine hydrobromide, are part of most premedication orders. The usual dosage in small children is 0.1 or 0.2 mg. For adults the dosage is from 0.4 to 0.8 mg. Both drugs are effective in suppressing salivary secretions, and to some extent also in suppressing secretions in the lower respiratory tract. Atropine, which is a racemic mixture of dextro-hyoscyamine and levo-hyoscyamine, is roughly half as effective as scopolamine on a milligram basis for the suppression of secretions. The levo-hyoscyamine fraction is the active ingredient and is commercially available. Excessive salivary secretions may occlude the upper airway and produce asphyxia or prolonged anesthetic induction time. However, the suppression of secretions in the lower respiratory tract may increase the viscosity of these secretions and result in atelectasis. Moreover, anesthetic agents such as thiopental sodium, nitrous oxide, and halothane do not stimulate the production of secretions. Furthermore, a properly placed cuffed endotracheal tube completely separates the mouth and pharynx from the tracheobronchial tree, thus eliminating any risk associated with salivary secretions. Therefore, proper utilization of modern anesthetic agents and techniques makes the use of the belladonna derivatives unnecessary, as a rule, at least for the control of secretions.

Another so-called desirable effect of belladonna drugs is blocking of the cardiac vagus in order to minimize the hazard of reflexes which might result in sinus arrest, cardiac standstill, and failure of ventricular escape in a drugged, diseased heart. As much as 1.2 to 2.0 mg. of atropine every 2 hours may be required to block the cardiac vagus. Whether such reflexes are really a hazard has never been established. The fact that, during anesthesia, atropine

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may reverse a bradycardia is not proof that the bradycardia was caused by a reflex. It can be demonstrated that a heart which is in bradycardia due to anoxia will respond to atropine with a brief tachycardia. It is certain that the usual doses of atropine administered once to block salivary secretions are inadequate to block the vagus. Rather than use very large doses of atropine a satisfactory approach to blocking reflexes is to anesthetize the sensing organ such as the carotid sinus or the hilum of the lung or the peritoneal cavity with a dilute local anesthetic agent such as procaine or lidocaine. Intravenous procaine or other local anesthetic agents are not recommended to suppress these reflexes. In addition one should monitor the heart with an *operating room cardioscope* and modify the conduct of anesthesia appropriately if arrhythmia should develop. If cardiac arrest should occur cardiopulmonary resuscitation preferably with closed-chest massage should be instituted immediately.

Atropine and scopolamine are not effective in the treatment of laryngospasm and evidence that they decrease the likelihood of laryngospasm is not convincing. These drugs may produce a tachycardia which is particularly hazardous in the cardiac patient and which once established cannot be effectively counteracted pharmacologically. Because they block sweating and may result in the retention of heat, particularly in children they should be administered cautiously in the presence of fever. They may produce some slight bronchial dilatation and thus increase the physiologic dead space of the lungs. Parenterally administered atropine or scopolamine usually does not aggravate glaucoma but consultation with an ophthalmologist is wise before subjecting the patient with glaucoma to anesthesia and surgery.

Reserpine. The patient who has received as little as one dose of reserpine within the 2 weeks preceding the administration of an anesthetic and surgical procedure may develop profound hypotension and bradycardia during or immediately after the anesthetic. Surgery should be deferred whenever possible. If surgery must be performed then atropine sulfate 1.0 to 2.0 mg preanesthetically may be helpful by increasing heart rate, in preventing this potentially dangerous response.

Digitalis. If a cardiac patient should manifest digitalis toxicity surgery should be postponed until toxicity has subsided. If this is not possible then an infusion of 40 mEq of potassium chloride slowly by vein may control ventricular irritability. If this is not adequate and surgery is urgent procaine amide, 250 mg intramuscularly may be used. If P-R prolongation or dropped beats are the problem however atropine may be of some help but one should be prepared to use an external cardiac pacemaker if necessary. Although underdigitalization may mean that cardiac contractility is not fully restored in the hospitalized patient the manifestations of congestive heart failure can usually be handled by ancillary measures, whereas digitalis intoxication may do irremediable damage. It would appear wiser to err on the side of underdigitalization at the time of surgery.

Barbiturates. A small dose of a barbiturate may be administered preanesthetically to a cardiac patient to allay apprehension. In practice apprehension is usually better managed by psychic reassurance and by confidence in the internist, suregon, anesthesiologist, and hospital rather than by 50 or 100 mg of pentobarbital the evening before surgery and the morning of surgery. Nevertheless in these small doses, untoward effects are unlikely. Neither cardiovascular nor respiratory depression would be anticipated even in severe cardiac disability. If the patient gives a history of allergy to barbiturates they should not be prescribed since the anticipated benefit is so little. Preanesthetic barbiturates are not needed to facilitate the induction of anesthesia. If the anesthesiologist should desire to produce amnesia for the experience of breathing anesthetic gases from a face mask, 100 mg of thiopental sodium intravenously at the time of anesthetic induction will usually produce amnesia. Barbiturates may tend to counteract to some extent the ventricular arrhythmias produced by such anesthetic agents as cyclopropane, chloroform and halothane. Barbiturates are of no value whatsoever in preventing the cardiovas-

cular toxic effect of local anesthetic agents, and in the usually administered doses are not even of value in preventing the toxic effect of local agents on the central nervous system

Narcotics Narcotics usually need not be administered preanesthetically to the cardiac patient Narcotics are analgesics, but cardiac patients are seldom in pain before surgery and after surgery their condition is usually precarious and would be adversely affected by the narcotics. The respiratory depressant effect of the narcotics can be counteracted by narcotic antagonists such as levallorphan which may introduce their own risks. During the administration of an anesthetic, the anesthesiologist can ensure adequate ventilation by assisting or controlling respiration but respiratory depression might be a problem in the postoperative period Narcotics interfere with the compensatory mechanisms of the peripheral vascular system. This is especially deleterious in the cardiac patient who is about to undergo the physiologic insults of receiving anesthetic agents, all of which depress the contractile force of the heart, and who also is being turned about and placed in unnatural postures and is having his tissues cut thus initiating a host of endocrinologic and neurologic responses and hemorrhage. Narcotics also suppress the cough reflex and produce somnolence both of which effects may aggravate a tendency to atelectasis and bronchopneumonia postoperatively

Antiemetic agents Antiemetic agents need not be routinely prescribed as preanesthetic medication for cardiac patients. Present day anesthetic agents and techniques are associated with an incidence of postanesthetic vomiting of between 5 and 10 per cent It is obvious that the agents would not be needed in the other 90 to 95 per cent. Should the patient vomit postanesthetically an antiemetic agent may be administered at that time.

Quinidine The cardiac patient may be on maintenance quinidine when he comes to surgery This can usually be continued Because of the variability of individual response to this drug institution just before operation is not desirable. Any irregularities that do occur should be treated in the operating room

Dietary fat and the general public

Since atherosclerosis is by far the leading cause of death in the United States, factors which may be of value in its treatment or prevention are of urgent concern, both to physicians and to the general public. A mass of statistical data indicates a definite relationship between elevated levels of serum lipids, such as cholesterol and triglycerides, and an increased death rate from atherosclerosis. Equally convincing evidence is available that a decrease in the dietary intake of hydrogenated fats, with substitution of polyunsaturated fatty acids, is associated with a reduction in serum cholesterol and lipid levels in most human beings. Long-range controlled studies are needed to prove that such a dietary regimen will reduce the mortality from atherosclerosis. However, it is a reasonable assumption that a reduction in serum lipids, if initiated early enough in the disease, will be beneficial. This emphasis in no way denies that other factors may also be of importance in the genesis of atherosclerosis. However, the existence of other factors does not relieve the physician of the responsibility of utilizing available knowledge to alter a condition which is known to be associated with increased mortality from atherosclerosis, even though knowledge of this entity is far from complete. The excessive mortality from this disease supports such an approach.

The Central Committee for Medical and Community Program of the American Heart Association and the Council on Foods and Nutrition of the American Medical Association[2] have independently taken cognizance of the possible association between diet and atherosclerosis and have provided lucid and informed guidance for the physician who desires to lower the serum lipids of his patients. Both reports emphasize that the recommendation do not apply to the general public. However, once the association between elevated serum lipids and atherosclerosis is acknowledged, a recommendation for alteration of the public diet is perceived as the only logical recommendation that can be supported. In view of this recognition of the association between diet and atherosclerosis, a statement that the public diet should NOT be altered is *undesirable because*:

1. The majority of patients who die from coronary atherosclerosis die before they reach a physician. Among active-duty personnel in the United States Army who died from coronary atherosclerosis, 60 per cent died before reaching a medical facility. The same is true in civil life. In the Framingham Study 77 per cent of the patients with initial infarcts who died within 3 weeks of the attack succumbed before reaching a hospital. Hence only persons with milder nonfatal cases can possibly receive dietary advice from their physician. Of those patients who reach hospitals alive, the majority of fatalities occur within the first day or two. These too, could not be benefited by a change in diet. Thus, the excellent dietary recommendations of the Central Committee for Medical and Community Program of the American Heart Association are denied to a large segment of the susceptible population—probably those who need it most.

2. Coronary atherosclerosis is practically a universal condition among adult American males. The United States Public Health Service supported an extensive cooperative study of cholesterol and lipoproteins as predictors of clinical atherosclerosis, in 15,000 American subjects. The conclusion was that there was a high statistical correlation between the blood levels of lipoprotein and cholesterol and atherosclerosis and its complications, but that such laboratory data were not of clinical use in predicting which individuals would develop coronary heart disease.

3. The Council on Foods and Nutrition of the American Medical Association included hypercholesteremia and hypertriglyceridemia as major indications for modifying dietary fat. It has been demonstrated by the Framingham and other studies that there is no level of serum cholesterol or other lipids at which the risk of developing coronary heart disease takes a sudden rise or fall, and no level that can be called normal. Since individuals with hypercholesteremia or hypertriglyceridemia do not consult a physician for these asymptomatic metabolic states, they are not readily identifiable. However, even if it were possible to identify all persons with these high serum lipid values, as defined by the Council, the dietary recommendations of the Council would still be given to only a small fraction of patients who die from atherosclerosis.

4. Since it is well recognized that coronary atherosclerosis is present for many years prior to the development of symptomatic coronary heart disease, it seems self-evident that a preventive approach is indicated. If efforts are to be made to alter the disease, logically they should be initiated before the process is far advanced. If the concept has merit that diet is a factor in the genesis of atherosclerosis, a recommendation to the general public for modification of diet has infinitely greater potential for benefiting the health of America than a recommenda-

tion to only the individual who seeks physician late in the course of his disease. Medicine has a responsibility to the public as well as to the private patient. Why not recommend to the entire susceptible population a modification of the diet based on the best scientific information available? A lesser recommendation is lacking in vision, because it offers less potential gain for the health of the American people and fails to recognize that the greatest promise of modifying the mortality from atherosclerosis lies in prevention. The only argument against such proposal is that final data which prove relationship between the reduction in serum lipid levels and the reduction in morbidity and mortality from atherosclerosis have not been accumulated. Although this is theoretically valid argument, there are several considerations which modify its general pertinence.

In the first place the lack of final statistical data does not prohibit the use of therapeutic regimens in medical practice. For example, corticosteroids, anticoagulants, and antihypertensive agents are in common use, although there is no unanimous agreement as to their ultimate efficacy in reducing mortality. Yet these agents are all infinitely more hazardous than a modest change in the American diet. There is no evidence that the recommended alteration is potentially harmful.

Secondly the evidence is already strong enough for the Central Committee for Medical and Community Program of the American Heart Association to recommend this diet for men whose personal and family histories suggest that they may be particularly susceptible to atherosclerosis, and for the Council on Foods and Nutrition of the American Medical Association to recommend dietary change for persons with hypercholesteremia.

We submit that, statistically the average American male will die from atherosclerosis, and therefore has history which suggests particular susceptibility to the disease. Furthermore, by world standards, he is hypercholesteremic and therefore meets the general criteria for dietary treatment. Must the young American male be forced to face the threat of sudden death before being offered this dietary advice

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Endomyocardial fibrosis and carcinoidosis. A common denominator?

It has long been suggested that the fibrotic heart lesion of carcinoid disease is due to a high level of serotonin in the blood The serotonin is synthesized in the argentaffin tumor and its metastases. In particular the chemical products of the liver metastases go directly to the heart, where damage occurs primarily on the right side. It is claimed that the serotonin returns to the left side of the heart after passing through the lungs where it is metabolized to 5-hydroxyindolylacetic acid (5 HIAA) by the lung monoamine oxidase.

It is of considerable interest, therefore, that in Uganda and some other tropical countries fibrotic lesion appears as common form of heart disease. This cardiopathy called *endomyocardial fibrosis* (EMF), has recently received the attention of an editorial in *Lancet*[1] in which the clinical aspects are discussed. The present paper is concerned with possible clue to the etiology of endomyocardial fibrosis. The disease becomes more interesting when it is learned that it often appears in areas in which the consumption of bananas or plantains, is high—

ndeed areas which the banana is frequently used as staple food. I East Africa the green plantain is peeled and then cooked by steaming wrapped up in banana lea es this food is called *matoke* and dults may eat between 400 and 800 grams of pulp at meal The banana tself contains large quantities of serotonin [18] and the association of fibrosis i the heart automatically raises the question whether there is common factor involved in carcinoidosis and EMF

A glance t the prominent distribution of this disease across Central Africa show that t is common around Kampala Uganda where the banana is used as the taple food It has not been seen to y significa t extent in Nairobi, Kenya, where the hospital is concerned with tribes from the rela tively dry plains, where banana growing is rare but further east, toward the coast the disease ppears, as does also the practice of banana eating [22] It is lso i teresting that as yet there is no recorded case n the Mulago (Kampala) utopsy records of EMF in Luo this tribe does not eat the banana on what might be described as "tribal grounds

On the West Coast of Africa the banana is again eaten It is frequently fed t children as milk substitute in the form of water-banana slush and here EMF is common manifestation of heart disease. Furthermore, as Foy nd Parratt[13] point out, the disease has not been found i the Europea population l ing in the same areas in which t occurs m the native population. Again it is not found in the Northern Regions of Nigeria where the habitual eating of plantain is not practiced. O the other hand this disease is rarely seen in Europe I one instance it as reported in person who had been prisoner of war i J pan.

Recently it was reported that East Africans living on normal matoke diet excreted high quantity of 5 HIAA the metabolite of serotonin. Indeed, the excretion rate of 5 HIAA was of the order of that seen carcinoid disease[23] (g 20 t 100 mg per 24 hours, the normal range being 0 to 10 mg per 24 hours) Shortly afterward this finding was confirmed by similar findings in West Africans.[24] That the African banana eaten by these various tribes contains serotonin has already been demonstrated nd the thor has recently shown that less tha 20 per cent of the serotonin is destroyed i the cooking process used by the people of Uganda —no 5 HIAA could be detected either colorimetrically or hromatographically in the matok. [25] That many natives of Uganda li on diet high in serotonin can be ppreciated from the fact that the daily diet contains some 30 to 100 mg of serotonin.[18] These figures correspond losely with the data obtained on the West Africa pla tain meals. Consequently the possibility that there is common factor i EMF nd carcinoidosis becomes qu te real

However there are three strong arguments against any relationsh p between serotoni and EMF First, the normal animal rapidly detoxicates serotonin.[17,1] Indeed, a clear distinction exists bet een the serotonin of carcinoidosis nd that of the banana-eating African I the instance of carcinoidosis the serotonin is, so to speak administered intravenously via the hepatic ein whereas in the case of the banana eater the serotonin has first of all to cross the gut wall and pass through the liver where it is normally metabolized. Secondly in endomyocardial fibrosis, both th left and the right sides of the heart are affected, whereas in carcinoid disease the lesion is, so far predominantly right-sided [6,16] Thirdly the lesions are claimed to be histologically different. [19]

These particular arguments, however are not necessarily final. First with regard to the metabolism of serotonin, it is true that the normal animal detoxicates serotonin rapidly But the normal animal is not subjected to the stress of life-long diet of serotonin nor the stress of malnutrition kwashiorkor and parasitic infections which re common in East Africa. The topsy records at Mulago Hospital show a greater umber of reported cases of EMF in persons in the poorer malnourished categories in particular it is prevalent among the Ruanda Burundi immigrant laborers.[26] Although the banana is not necessarily the staple diet of the Ruanda Burundi tribes, it is frequently the adopted food largely because of its vailability nd prestige value, since the matoke is the staple food of the employers, the Baganda. Also, it is nlikely that the Ruanda Burundi who come to autopsy t M lago are recent immigrants. They have often lived in the Kampala area for considerable time and frequently dopt the ways of th Baganda.[26]

The feeding of bananas, which re virtually protein free, t children is often th dietary cause of infantile malnutrition. It is also known that kwashiorkor is associated with disturbances in liver function and nitrogen metabolism.[27] [28]

Thus, i regard to the first argument, it must be remembered that w are dealing with population many of whom are on diet that is chronically high in serotonin and among whom there is high incidence of parasitic infections, tuberculosis, and malnutrition. Therefore we need not be dealing with biologic normality in the accepted sense. Indeed one might expect the very conditions prevailing particularly when they affect liver function, to gi rise to abnormalities in metabolism. Recently an increase in the excretion of serotonin has been reported in red cell plasia associated with inf tile mal utrition.[29] Increased excretion of serotonin has also been reported in bilharziasis.[30] Again, the chronic dministration of serotonin in experimental animals has been shown t give rise to reduced amine oxidase activity and increased platelet cou t.[31,32]

An answer t the second argument in regard to the localization of the carcinoid lesion in the right side of the heart, in contrast to the occurrence of the EMF lesion on both the left and the right sides, follows on from the foregoing discussion. Either chronic serotonin feeding is sufficient t produce increase in blood serotonin, or n increase in blood serotonin would be produced by defect in or i hibition of its metabolism. If dietary serotoni is responsible for the fibrotic lesion it is likely that defect in metabolism plays a vital part since under normal conditions the serotonin will be mostly destroyed on passage through the liver Since lung metabolism is the reason for the carcinoid lesion occurring essentially on the right side, it is

clear that, in the presence of defective metabolism serotonin would not be expected to produce a lesion on one side only. Indeed, taking the argument a step further, impairment of endogenous serotonin metabolism might be all that is necessary without the added hazard of a diet of bananas for the production of a lesion. It may well be possible that enzyme defects in malnutrition could have more serious consequences than dietary serotonin alone.

It is of interest that the lesion of the carcinoid disease also appears on the left side of the heart, although admittedly it occurs predominantly on the right side. Thorson in a collected series of 33 cases of carcinoid in which the left side was examined found 12 macroscopic valvular lesions, and out of 24 cases, 5 mural lesions. These lesions were all grossly visible. Thus it can be said that not only does the carcinoid lesion appear on the left side of the heart, but, also, one would expect a lesion produced by dietary serotonin to occur on either the right or the left side.

Thirdly, the question of the distinctions between the cardiopathies of carcinoidosis and EMF is difficult to evaluate since one cannot say whether the result of high-level acute sporadic insults would be the same as that produced by a low-level chronic insult. There can be little doubt that these cardiopathies are different entities. However, Thorson, while distinguishing quite clearly between a number of fibrotic heart lesions and that of carcinoid, says, "The structure of the lesions of this disease (EMF) is rather similar to that seen in carcinoidosis. However, the curious prevalence for Negroes, the more rapid course of the disease and the different localization of the lesions in endomyocardial fibrosis, speak against a common denominator." The right/left distribution of the lesion of EMF need not be valid differentiation. However, the predominance of the lesion of EMF to the inflow tract and that of carcinoidosis to the outflow tract may be a most significant feature, and further histologic analysis is eagerly awaited.

The evidence suggests that serotonin by itself is not of importance. On the other hand, malnutrition by itself is not the causative agent, otherwise the disease would be found in central Kenya and Southern Rhodesia (where autopsy is obligatory) and other places where malnutrition is a serious problem. This again comes back to the problem of malnutrition in association with the banana. In this connection it is curious that EMF does not seem to occur in Jamaica, where there is both malnutrition and the eating of the banana. However, there is at least one interesting difference between Jamaican and Uganda banana eaters. The Jamaicans boil the banana in water and this method of cooking elutes and destroys most of the serotonin, whereas the steaming practiced in East Africa destroys only a small fraction of the serotonin. This is mentioned only to point out that apparently trivial points could be of significance. Habitual matoke eaters are occasionally found to excrete significant amounts of serotonin after a test meal of 100 mg. of serotonin.

The synergism that exists between the dopamines and serotonin may be of importance, since the dopamines are present in both the banana and many vegetables. Of particular interest is the report that subdermal administration of serotonin and dopamines together produced petechiae and hemorrhage in rabbit skin and cyanosis in the human skin, providing a possible mechanism for damage.

It is clear that acute oral administration of these pharmacologically active compounds has no effect on the healthy animal. However, it is also evident that it is not unreasonable to expect that conditions will arise whereby pharmacologic action could be observed by oral administration. In this connection the high local incidence of adult intussusception and keloid healing may be important.

The clue of the banana eaters may be misleading but this clue, together with the over-all distribution across Africa, make the investigation of dietary factors in the vegetable and fruit kingdom a reasonable starting ground. Serotonin analogues and precursors should not be overlooked. It would be of interest to know the incidence of EMF in tribes using the root crops as staples (e.g., yam, sweet potato, and cassava), the indole nucleus being used in the root growth hormone might be expected to be found in the root crops. Potentiation by other compounds should also be considered, especially competition for sites of loss by the amine complex. At the same time this disease could be caused by a specific deficiency. It is appreciated that the speculations are endless and need not be confined to toxic agents or deficiencies. Apologies are made that this paper is essentially concerned with one speculation. But an attempt has been made to point out that careful analyses and investigation is required before conclusions can be reached. At the moment there is no convincing evidence either for or against the possibility that there is a common denominator between EMF and carcinoidosis.

It is now essential to have a clear histologic definition of EMF so that the disease may be compared more readily with the cardiomyopathies seen in other parts of the world. Is it possible to say that the lesion of EMF is produced by a toxic factor or is it a deficiency disease? A diagnostic technique in life is needed so that an adequate survey of the incidence of the disease can be made. It is particularly important to establish the local variations in incidence in East and West Africans, both by clinical assessment and autopsy confirmation. For example, EMF has been reported in the Sudan, and yet the diet there would appear to be quite different. The terminal state in which the disease is seen in most Africans may well have its cause buried in the past history. Unfortunately, proof of EMF can so far only be obtained post mortem, and the cadavers are not inclined to impart much information in regard to their past history.

The need for information now is particularly important, because, as the pattern of existence in tropical countries changes, a vital clue in regard to the processes involved in fibrosis may be lost.

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On the lack of meaning of heart failure

Failure is an abstract polar term which lacks meaning unless qualified by the specific accomplishment or performance that has been omitted. The term "heart failure" or the statement "The heart failed" is as devoid of meaning as is the term "heart accomplishment" or the statement "The heart accomplished." The reason that the two former terms do have meaning to physicians and to lay persons is that, by common usage over centuries, hydropsy or dropsy recognized for instance by Job Milton and/or shortness of breath, recognized for instance by Sir Walter Scott as a precursor to dropsy are

implied as manifestations of the cardiac state "heart failure."

However, just as we know that there are many causes of dropsy and of dyspnea other than cardiac function, so there are as many types of cardiac failures as there are cardiac functions. The most important ones (from the patient's standpoint) are those that make him sick and shorten his life.

Even a short stay in the cardiac catheterization laboratory will teach the physician that the left ventricle may fail to reach a normal end-diastolic pressure and yet the heart may keep the body free (as far as present-day measurements) of dropsy and maintain normally many other cardiac functions and ratios of functions. Such ratios may represent ventricular function curves, but no single one has the inherent right to be called *the* ventricular function curve.

Braunwald and Ross[1] state "the precise manner of recognition of the heart failure state, by hemodynamic means, is of course dependent on the manner in which one chooses to define this circulatory state." Perhaps the best test of their conceptual thinking is their failure to proceed to define the heart failure state from hemodynamic findings. Such failure is not excused by jumping to a hypothetical method of assessing "the mechanical function of the ventricle. The hemodynamic findings reveal in what ways, if any, the heart has failed to respond in a normal hemodynamic manner. The significance of these failures is determined by longitudinal studies of patients and by changes in many functions after the hemodynamic abnormalities are reduced or are restored to normal.

That the end-diastolic pressure of the left ventricle can be raised by overdistending this chamber or by blocking its exit is well known. To assume that under such circumstances the left ventricular myocardium is not failing in many ways is a verbal myth engendered by the nonsense, unqualified term "heart failure" and the unwillingness of the investigator to acknowledge that the heart may fail in many different ways under different types of stresses.

Treatment is indicated if it is feasible to remove the factor or factors which have caused the heart to fail in functions which are vital to a patient's health. From a conceptual standpoint, all such factors can be regarded as external to the contractile elements of the heart, except for muscular dystrophies, and even some of these may be due to external factors.

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The singularity of man: A major problem of therapy

Recently, increasing attention has been directed to the large number and seemingly infinite variety of medicaments available to the practicing physician, including the cardiologists. Although some controversy exists relative to the exact number of such medicinal products, there is unanimity in the recognition of the problems posed by the superabundance of therapeutic agents. This is particularly true since in many instances these are identical compounds which differ only in trademarks and costs. In other instances the substances are, for all practical purposes, pharmacologically identical but possess minor chemical structural differences sufficient to warrant individual patent rights. Confusing as these circumstances are, the situation is further complicated by inadequately controlled, often meaningless clinical trials. Scientifically designed and oriented drug evaluation, although becoming more common, is still too infrequent, and one of the most difficult investigations to conduct adequately. Too often, clinical evaluations of drugs are relegated to physicians who have never had any training in the discipline of research—which is a serious handicap at the outset.

Recognition must also be given to still another major problem which confronts the clinical therapist, i.e., man, the test animal. The clinical evaluation of any pharmacologic agent must take account of the singularity of man, in all of his compensatory emotional and situational reactions. Attention must be directed to those unique attributes of man, e.g., memory, psychophysiologic reactivity, judgment, which, by their continuous and ubiquitous function, modify responses to pharmacologic agents. To a larger extent, the problem may be better appreciated by consideration of the placebo response in all of its ramifications.

Although physicians have used placebos since time immemorial, reference to the placebo as such has been uncommon until relatively recently. In 1945 Pepper[1] noted his inability to find any prior reference to the placebo phenomenon in the *Index Catalogue of the Library of the Surgeon General's Office* and the *Quarterly Cumulative Index Medicus*. Nevertheless, individual clinical investigators have frequently had recourse to the placebo. Thus, in three sequential investigations over a period of 10 years, Diehl[2-4] utilized placebos in evaluating various

medications used in the treatment of the common cold. With the help of the placebo these investigators were able to show the lack of benefit derivable from multivitamins and from many of the commonly used cold remedies. Probably of equal significance was the demonstration that approximately 7 per cent of the subjects who received saline placebos in the vaccine study complained of untoward symptoms attributable to the vaccine and that a small percentage of subjects who received oral lactose placebos experienced "toxic symptoms." Similarly, Wolf and Pinsky, incident to the evaluation of a mephenesin, encountered untoward reactions to the lactose placebo. In several instances these complications were of considerable magnitude. Striking is the experience of Tucker, who reported that in the placebo group of a streptomycin study project, 61 per cent of the subjects experienced one or more of the commonly accepted complications of streptomycin therapy. Loss of high-tone and low-tone hearing, eosinophilia, and impaired urea clearance were among the undesirable effects of the placebo. In fact, from an analysis of many clinical studies of drugs in which lactose was used as the control, one would be forced to conclude that lactose is the most effective drug for treating most of the diseases and symptoms of mankind. Thus there is ample documentation of the negative as well as the positive response to the administration of placebos. It follows that not all toxic reactions to pharmacologically active agents can be attributed to the drug.

In an attempt to define more clearly the character of the placebo response, Lasagna demonstrated that the placebo may mimic the kinetics of treatment with active agents. Using a placebo in patients with tuberculosis, ostensibly to instill a feeling of "pep and energy," he clearly demonstrated the development of a cumulative effect attributable to placebo therapy. In that portion of the investigation which dealt with postdelivery analgesia treated with either aspirin or placebo, he showed that the response curves to each of the agents paralleled one another, although there was a greater incidence of response to aspirin. Accordingly, placebo therapy must be recognized as capable of inducing cumulative effects and of paralleling in the time course of its response, pharmacologically active therapy as well as acting as the source of untoward or toxic reactions. Such characteristics make extremely difficult the evaluation of any therapeutic agent. Moreover, in addition to the intrinsic actions of the placebo there are extrinsic factors which may affect human response to therapy. Such factors have been studied by Wolf over the course of many investigations. In essence, he has demonstrated that drug response may be determined by conditioning of the patient, circumstances of drug administration, and physiologic status of the organ at the time of therapy.

What of the responder to placebo therapy? How can we identify and characterize him? Unfortunately such knowledge is incomplete at this time, although Lasagna's study of the placebo response to postoperative pain provides valuable information in this area.[7] Interview data obtained from ward personnel and from the patients themselves in conjunction with various psychometric tests, revealed the reactors to have experienced less postoperative discomfort and pain than have the nonreactors, to have requested medications less frequently, and to have been more cooperative and more pleased with their medical care. As a group, reactors had a higher incidence of dysmenorrhea and more somatic symptoms under stress. They could be characterized as more emotionally expressive, recipients of less formal education, and less frequently active churchgoers than the patients who did not react to placebo therapy. Although the nonreactor group showed less deviation from the normal than the reactor group, they were noted to be far more rigid and emotionally controlled than the average person of the same age and background. The possibility was raised that the rigidity of the nonreactors might represent an excursion of their defense mechanisms in a stressful situation. Of considerable import was the finding that there was a significant number of inconsistent responders, which is attributable in part to variation or intensity of pain and to pharmacologic sophistication, i.e., the ability to distinguish between the active and the inactive agent after repeated exposure to both agents. These problems in the study of the influence of drugs on pain are well exemplified in the case of angina pectoris. One of the more unfortunate aspects of improper study and premature use of new drugs is the displacement of older agents of established efficacy by ineffective compounds, often with serious consequences.

When viewed in the light of the foregoing discussion, the vagaries of human response to therapy are no more distinct but considerably more palpable. The importance of further investigations along these lines is obvious. Equally manifest is the value of Alexander Pope's dictum: "The proper study of mankind is man."

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Special report

Review of papers and discussions presented at the Symposium on Pulsatile Blood Flow

Résumé prepared by
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The first International Symposium on Pulsatile Blood Flow* was held April 11-13, 1963, at the Presbyterian Hospital, Philadelphia, Pa. The rapid progress in theoretical approaches to and the wide interest in a dynamic analysis of blood flow called for a meeting in which the progress of the last few years could be reviewed, the present state of our knowledge of the field re-evaluated, and existing problems and their possible solutions outlined. The results of this conference, which was attended by physiologists, engineers, mathematicians, and physicists from Australia, Czechoslovakia, England, Holland, Russia, Sweden, Switzerland, and the United States, can be summarized as follows.

A. Instrumentation. The transducer recording systems, used for an accurate evaluation of pulsatile flow, must meet considerably higher requirements than those which are generally considered to be satisfactory. A flat frequency response from 0 to 30 c.p.s. is absolutely necessary. The present state of manometry and displacement measuring devices is probably adequate, provided that extensive care is exercised for both their static and dynamic calibration. The damaging effects of minute air bubbles on manometer behavior are still not generally realized.

The performance of flow metering devices, on the other hand, is far from satisfactory. Two main problems must be solved before both the electromagnetic and the ultrasonic flowmeters can be used with confidence for such studies. Although the calibration of their electrical performance can be carried out with relative ease, the dynamic calibration of the whole electromechanical system is fraught with difficulties. Adequate volume displacements at the required frequencies necessitate powerful pumps, the output of which must be exactly known. Although such devices can be built, they are likely to be considerably more expensive than the flowmeters themselves.

The second problem relates to our ignorance about the distribution of velocity profiles in various types of flows and cross sections. Theoretical considerations indicate that errors of up to 25 per cent may be introduced if the velocity profile used for the calibration is significantly different from those actually encountered during the experimental measurement. Additional questions which are at present not too well understood include the effects of hematocrit, wall thickness, temperature, blood chemistry (ionization), vessel fit, field frequency, and wave shape, electrode character, and contact potential upon flowmeter performance.

Since minor errors in amplitude and phase lead to significant differences in some of the calculated parameters, a better understanding of these effects is absolutely

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essential for a reliable interpretation of observed results. Considerably more theoretical and experimental work is necessary before these effects can be properly evaluated.

B. Theoretical and experimental approaches to pulsatile flow. The flow of blood through the vascular bed depends only upon two parameters, namely, the driving pressure and the impedance of blood and vasculature. The driving pressure is of course provided by the pumping action of the ventricles so that the impedance describes the over-all behavior of the vascular bed and its content and includes explicitly the inertial and viscous properties of the fluid as well as the physical characteristics of the vessel wall. A theoretical analysis of this behavior was carried out by Womersley only a few years ago and experimental results presented at this meeting indicate that Womersley's theory underestimates the frictional losses in pulsatile flow. These differences may be due to the fact that the individual vessels taper, that turbulence is present during at least part of the cardiac cycle, and that the vessel wall is viscoelastic. A powerful analysis of the tapering effect was presented. This approach is very promising; however, a number of refinements are necessary until the predictions resulting from this theory are as good as those obtained from Womersley's work. In uniform elastic tubes the pressure-flow behavior can be predicted by classic theory. As soon as nonuniformities such as changes in wall thickness, vessel diameter, or branching are introduced, the observed results become quite different from those expected from theory even in relatively simple models. The nonuniformity of the vascular tree is not limited to geometrical factors alone but includes progressive stiffening of the vascular wall toward the periphery. There are significant species differences present in this regard so that the *Windkessel* might be an appropriate model for the domestic turkey but quite unsatisfactory for mammals. Few quantitative data on the behavior of smooth vascular muscle are available at present, but its influence upon the physical properties of the vessel wall may account for an increased pressure wave transmission in the smaller blood vessels.

The flow of blood through the vessel wall is another factor which has been neglected until recently, although it is well known that coronary blood flow changes widely from cardiac systole to diastole. Similar effects may be expected in the arterial wall and result in variations of its mechanical behavior. Model experiments in tubes with circular and elliptical cross sections indicate that even minor deviations from a circular cross section may introduce serious inequalities in the distention of viscoelastic tubes. These inequalities reach a maximum in the ellipse where the two semiaxes change in opposite directions during the pulsatile cycle. Further investigation is necessary to determine how far these results apply to various vessels in situ.

In hydrodynamics the Reynold number defines the ratio between inertial and viscous forces and its critical value, a condition which is necessary to maintain turbulence. This condition can, however, only be evaluated if the flow channel is long with respect to its hydraulic depth. In the vascular bed this ratio is quite small and it is of minor importance, therefore, whether the introduced disturbances maintain themselves or die out after having traveled a certain distance, since new disturbances will already have been introduced over this interval. Birefringence studies indicate that, in pulsatile flow, turbulence in tubes of the size of the larger vessels appears already at mean velocities of 20 to 30 cm. per second, i.e., values which are certainly exceeded over most of the systolic part of the cycle. Additional turbulence is introduced at any branch point. Measurements of pressure gradients at these flow rates in distensible tubes indicate that the turbulence observed by the birefringence technique may alter the pressure-flow relations considerably. The production of turbulent flow in pulsatile flow depends not only on the hydraulic depth, kinematic viscosity, and mean velocity but on the frequency and amplitude of the superimposed oscillations as well as on the physical properties of the wall. For an evaluation of the latter, the shape of the actual cross section has to be considered.

These problems are as much of a challenge to the mechanical engineer and hydrodynamicist as to the vascular physiologists. Powerful methods are available for

their study but they require not only exquisite instrumentation and extensive computer facilities, but multidisciplinary man power as well This Symposium has been another demonstration of the advantages to be gained by combining several disciplines into one team provided that the problem is properly defined

The proceedings will be published late this fall by McGraw Hill

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Letters to the Editor

Hematocrit, hemoglobin level, and coronary heart disease in the South African Bantu

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To the Editor:

In an Editorial entitled "Hematocrit, Blood Viscosity and Myocardial Infarction," Burch and De Pasquale[1] summarized evidence which suggests that high hematocrit levels adversely affect blood viscosity and might predispose to thrombosis in diseased arteries, especially in the vicinity of narrowed segments. They indicated that when the hematocrit exceeds 50 per cent, viscosity increases disproportionately. More recently, Stokes[2] has speculated on the role of hematological factors as related to the sex difference in coronary heart disease and has suggested, *inter alia*, that "the higher packed cell volume in men could encourage mural thrombus formation by altering the flow characteristics of blood, and may largely explain the sex difference in coronary artery disease." He continued that "if this is valid, then men might enjoy the same low incidence of coronary artery disease as women if their hematocrit could be consistently maintained near 40 per cent." In an interracial study undertaken at three widely separated centers, namely, Portland, Tokyo, and Memphis, it was considered that hematocrit was directly related to serum cholesterol in all subjects studied. At the 110th Annual Meeting of the American Medical Association (1961), Birnbaum and Levein[3] suggested that "there is aetiological significance in the observation that rates of coronary heart disease within certain populations vary directly with the haemoglobin levels of these populations."

The introduction of yet a further factor believed to influence coronary heart disease (CHD) raises the query whether elevated hematocrit and hemoglobin levels simply are accompanying components in a nutritional context favoring CHD or whether they exert their influence specifically.

Geographically, Johannesburg is well placed for testing purposes. The high altitude (6,000 feet) causes hematocrit and hemoglobin levels to be higher than at sea level. Locally, Lowe[4] found the mean hematocrit value to be 50 per cent and the hemoglobin level, 17.7 Gm. per cent, for a group of outwardly healthy white males. Among the local African Bantu population, in addition to the effect of altitude, there is the influence of the intermittent high intake of iron, and of siderosis, which is present in 70 per cent of the males over 20 years of age. Hence among this relatively underdeveloped and economically poor population there is a much greater proportion with high hematocrit and hemoglobin levels than among an otherwise similar population elsewhere. For example, in one series of 46 *indigent* Bantu male pensioners over 60-100 years of age, the mean hematocrit was 43 per cent; 13 per cent of the subjects had values of 50 per cent or more; the mean hemoglobin level was 15.2 Gm. per cent. In another series, in this instance of better-class Bantu over 40 years of age, the proportion with high hematocrits was 34 per cent. These are the people that Professor J. N. P. Davies called the men of "blood and iron."[6]

The salient question at issue is whether a high hematocrit level per se (with the associated ramifications) causes or promotes CHD. The problem can be approached perhaps most readily by considering the local Bantu. Exhaustive investigations, clinical (with ECG studies) and pathologic, as well as detailed follow-up studies of affected patients,[7-9] testify uniformly to the rarity of proved myocardial infarction in these people. Although death certificates suggest a higher figure,[10] it is very much doubted whether there are more than, say, 10 deaths from CHD per annum in Johannesburg among a Bantu population that approaches 600,000, of whom at least 50,000 are over 65 years of age. The explanation may well be, as implied by Burch and DePasquale, that high hematocrit levels are likely to be noxious only in the presence of diseased arteries with narrow segments. In the most recent local paper bearing on the subject, Reef and Isaacson[11] reported very little atherosclerosis of the coronary arteries, and possibly still less in the cerebral arteries, of Bantu dying in Johannesburg.

The urbanization of the Bantu, with associated sophistication of diet and manner of life, has been proceeding for some time, especially during the last two decades.[12] But information suggests that the intermittently high intake of iron (mainly adventitious from utensils used in fermented cereal preparations[13]), with associated high hematocrit and hemoglobin levels and siderosis,[14] has been prevalent for a far longer period. It is apparent, therefore, that sustained unusually high hematocrit and hemoglobin levels per se, whether in a primitive population or in one in the process of becoming westernized, neither has caused nor predisposed to mortality from coronary heart disease.

The foregoing, of course, does not imply that

high hematocrit or hemoglobin levels are irrelevant in regard t CHD The noxious effect of influencing factor may well depend on the total context of diet, environment, manner of lif etc. I other words factor may be deleteriou in one context yet pparently innocuous in another For example there is evidence which suggests that high intake of f t by somewhat primitive populations need not necessarily be associated with high incidence of CHD [21,22] The same pplies t hypertension.[22,23]

There is however one aspect of the Bantu which possibly ma be germane t the subject. Swank[3] has correlated blood viscosity not only with hematocrit but with erythrocyt sedimentation rate. Now high ESR alues are extremely common among the Ba tu [23] as with similar populations which ha high prevalences of infections in blood and stools. Normally in such populations, high ESR values are associated with lowered hematocrit levels. Among the Bantu, however it is not uncommon to hav high hematocrit simultaneously with a high ESR alue in the same subject Plenty of adult carry out their everyday work with ESR alues habitually high e.g 20-40 (Wintrobe scale, ncorrected). It would be illuminating therefore, t determine whether high ESR alues in these people re associated with favorable blood iscosity (and hence have bearing on their freedom from CHD), despit the simultaneous prevalence of high hematocrit levels

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To the Editor

In the January 1963 issue of the American Heart Journal there ppeared an interesting letter to the Editor by Dr Prinzmetal. H mentions the controversy and lack of conclusive evidence in the saturated versus unsaturated-fat effect on hardening of the arteries. Goat milk is mentioned as being high in nsaturated f tty acids, but economically unfeasible as a substitut for cow milk.

Dr Prinzmetal notes that the American public likes dairy products and likes these products t possess the sa ory qualities of milk fat. In iew of these preferences, he suggests breeding program to provide cow genetically endowed with the ability to produce milk that is high in unsaturated fatty acid content.

This is an excellent *suggestion nd is genetically* possible for long-term project. However the problem (if such problem exists) to provide more unsaturated f tty acids the milk fat can be more quickly solved by dietary means. When reasonable evidence exists that more unsaturated fatty acids are necessary *the dairy industry can quickly* con vert to such production and then reinforce this property by long-term breeding program.

The composition of milk fat depends l large measure on what the cow has been fed. For example cow fed fresh green feeds tend to produce milk fat with more unsaturated fatty acids. Linseed oil feeding can almost double the iodine umber of cow milk f t.

The iodine number of dairy milk fat reported by several different investigators varied from 27 9 t 46.9 These variations are to be expected because of the mple evidence that the haracter of feed influences the composition of the f t produced from it. Other variables that ca affect the fatty acid composition of milk are climatic or seasonal changes differences in stage of lactation, and plane of nutrition

Finally according to vailable information, goat

milk fat does not necessarily ha e a greater degree of unsaturation tha does cow milk. The propor tion of saturated fatty acids has been reported to be 60 per cent for cattle and 71 per cent for goats For the unsaturated f tty acids, the cow show 37 per cent monoethenoid fatty acids as contrasted to 25 per cent for the goat 3 per cent diethenoid (cattle) to 4 per cent (goat) and, finally cattle show 1 per cent triethenoid fatty acids whereas that of goats is insignificant.

The components of milk fats av ailable i the market place deserve consideration, because phospholipids carry the greater proportion of the unsaturated fatty acids that occur in hole milk. In cream separation, about 30 per cent of the phospholipids remai in the skim milk nd 70 per cent in the cream. Of this 70 per cent of the phospholipid content, about 45 per cent remains in the sweet buttermilk nd 55 per cent in the butter The melting of butter to obtain butterfat removes the rest of the phospholipid content, which is now found in the butter serum. Terms like *milk fat butter* and *butter fat* ar not 1 y interchangeable and comparisons should be made with caution

It is obvious that variations in reports and comparisons reflect the local conditions here those tests were made. If there ere demand for specialized milk fat, the dairymen could quickly change their feeding processing and marketing programs to meet the demand.

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T the Editor

I should like to comment on the Annotation, I terference Dissociation nd Semantics A Plea for Rational Nomenclature by Brendan Phibbs, which ppeared in the February 1963 issue of the AMERICAN HEART JOURNAL (p 283)

The argument centers around the term nterference as introduced by Mobitz in 1923 hen he clarified hitherto ill-understood arrh thmia hich he termed I terferenzdissoziation.

According to Phibbs, Mobitz coined the phrase Interferenzdissoziation to describe trioventricular dissociation caused by the discharge of an ectopic pacemaker Mobitz did nothing of the sort I his outstanding paper entitled Zur F age der trioventrikulären Automatie (On the Question of Atrioventricular Automatism) he coined the term to describe an arrhythmia hich he established as epar te entity and to hich he ga this name Phibbs rote Although the phrase miteinander interferieren is little ague there is no escaping the fact that the author is talking about the se of the dissociation, the interference set up by th trioventricular nodal pacemaker hen he calls the arrhythmia 'interferenz-dissoziation, and that h specifically chooses this term to differentiate the arrhythmia from trioventricular block (p 266) This interpretation of Mobitz ork is entirely f llacious. The phrase miteinander interferieren is not t all vague for those ho are familiar th the subject ith the other paper hich Mobitz published in the same year (hich Phibbs does not mention t all), and ith other ork of that period.

The essential point is that Mobitz wrote bout the interference of tw RHYTHMS and NOT about the interference of tw impulses That interference of tw RHYTHMS is meant is proved by the fact that *all* his examples refer to cases of entricular arrhythmias due t premature beats, hich he showed to be conducted S-A beats, including cases of others hich he correctl reinterpreted in this w y (cases of Wenckebach Taschenberg Edens). This is also evident in his diagrammatic Figure 8 (p 281) Wenckebach in his analysis of the ery case which Mobitz orrectly reinterpreted subsequently used the term *interference*" in the same sense of interference bet een tw rhythms die echte Vorkammer arbeitet uf eigene Hand ihre Tätigkeit interferiert mit der Tätigkeit des übrigen Herzens (p 349) (the right atrium orks independently its activity interferes with the action of the rest of the heart)—which interference Wenckebach interpreted as extrasystoles. I 1907 in discussing Interferenz zweier Venenrhythmen he wrote Ist es der Herzschlag nicht zu frequent und die Dissociation an der Vene ziemlich vollständig so wird es zu einer Interferenz der beiden Rhythmen kommen, welche sich kurze Zeit in einem doppelten Rhythmus äussern kann, bis schliesslich der eine Rhythmus siegt (p 8). (If the heart action is not too fast, and dissociation on the ein fairly omplete interference bet een the t o rhythms ill result, hich may manifest itself in redoubled rhythm for a short time ntil eventually one of the rhythms ins.) I the same paper Wenckebach lso wrote bout surprisingly regular interferences after four to six regular beats. The case of 1906 was included by Wenckebach in his classic monograph of 1914 as Dissoziation der Vorhoftätigkeit I terferenz zweier Vorhofrhythmen (p.100).

That Mobitz used the term interference with this connotation is also evident in another paper he published in the same year (1923) significantly entitled Über die verschiedene Entstehungsweise extrasystolischer Arhythmien beim Menschen ein Beitrag zur Interferenz mehrerer Rhythmen (On the Different Modes of Origin of Extrasystolic Arrhythmias in Man, Contribution to Interference), which Phibbs seems to ignore. Mobitz wrote An interpretation as interference despite the constancy of the couplings seems justified because, in this instance we can deduce the rhythm of the activity of both centers directly from the tracing without any calculation (p 493). "We recognize dissociation—these are by far the commonest cases—by the independent activity of two parts of the heart occurring in different rhythms, which we record directly or which we can deduce by analysis through calculation of the irregular sequence of beats of a part of the heart which we resolve as interference of several regular rhythms (p 491) In all instances of interference which have come to our knowledge so far the rhythm which becomes manifest only in occasional beats is the slower one In interference-dissociation this is invariably the sinus rhythm. It ranges above the basic rhythm of the tracing and as soon as it extends to a subordinate part of the heart, results in a shift of the heterotopic rhythm A protective block of the subordinate center exists here solely by the interposition in the path of spread of sinus stimuli of refractory parts of the heart during and shortly after their stimulation. This kind of protective block therefore arises out of a universally accepted principle of cardiac physiology without [the necessity of] any further assumptions. (The foregoing is my translation the original is given in Appendix A.) Here, Mobitz DID use the term Interferenz when discussing the conditions in which an interfering rhythm became manifest he DID NOT use the term where in the electrophysiologic sense it would have denoted the abolition of the effect of an impulse due to refractoriness. Phibbs deduction from Mobitz phrase Interferenzdissoziation mit Verkettung (interference-dissociation with linkage) that Mobitz used the term "interference in the electrophysiologic sense is incorrect All that this phrase means is that, by the interference beats, the two rhythms are linked because the interference beats, by discharging the A-V pacemaker produce a shift in the A-V rhythm. Dissociation with interference but without a shift in the A-V rhythm, was reported in an observation in animal experiments by Rothberger and Winterberg Their work was discussed as one of two varieties of this arrhythmia, under the subheading of "Die Dissoziation mit Interferenz ohne Rhythmenverknüpfung (dissociation with interference without linkage of the rhythms) by Wenckebach and Winterberg Here again, the salient feature is the interference of one RHYTHM with another RHYTHM whether with (Mobitz Interferenzdissoziation) or without shift of the A-V rhythm.

In the same paper Mobitz contrasted Interferenzdissoziation with Parasystolie and suggested the criteria for distinguishing these two arrhythmias which are both characterized by irregularities of the ventricular rhythm due to effective impulses arising in another center this is a further clear indication that, by "interference, Mobitz meant interference between two rhythms.

Furthermore the term Interferenz has been used in the same sense as interference between two RHYTHMS in other arrhythmias in which two or more centers produce cardiac contractions Extrasystolen als Interferenzerscheinung (Singer and Winterberg 1920) (extrasystoles as a manifestation of interference) Ventrikuläre Parasystolie durch einfache Interferenz (ventricular parasystole by simple interference), a term going back to Singer and Winterberg paper and accepted by Wenckebach and Winterberg (1927), Rothberger (1931), Scherf and Boyd (1953), and Holzmann (1960). In all this work by the pioneers investigating arrhythmias, the term Interferenz has been and is still being used with this connotation. Such interference of two rhythms becomes possible because of the dissociation, and, for this reason Scherf (1926) in accordance with Wenckebach rightly suggested for this arrhythmia the term dissociation with interference (instead of interference-dissociation).

There is no reason whatsoever why Mobitz should have used the term "interference in a sense entirely different from that in which the most competent authors in this field used it both before and after his papers 1923

The term originated from observations of arrhythmias in animals, and Mobitz reports are the clinical counterpart of those observations Hence Cushny (1897) "Thus we may have an interference occurring in the ventricle from the clashing of the auricular and ventricular rhythms while the ventricular impulses are unable to pass to the auricle, and the latter therefore beats perfectly regularly (p.279). "The periodic irregularity of the second stage is then due to the interference of the two rhythms of the heart (p.281). And Rothberger and Winterberg (1912) In the further course of events, with the more rapid reduction of the ventricular rate the number of conducted atrial beats steadily increased, different forms of allorhythmia result depending on the interference between the two rhythms (p.416). (The foregoing is my translation the original is given in Appendix B.)

There is no reason to depart from the definition of atrioventricular dissociation as commonly used and universally understood defined by Lewis as completely independent action of auricles and ventricles, or more explicitly as applicable to all arrhythmias when the ventricles are controlled by a ventricular pacemaker and the atria by an atrial pacemaker That A-V dissociation is always present in complete A-V block and that A-V dissociation may occur independently of complete A-V block is irrelevant in the present context, nor does it give rise to any confusion for anyone even faintly familiar with arrhythmias the various grades and types of A-V block are too well known to warrant any reappraisal. No. 3 of Phibbs suggested classification, which states that "The term interference-dissociation is to be used to indicate dissociation of atrial and ventricular rhythms caused by the discharge of an ectopic pacemaker is entirely misleading

since it could include in "interference-dissociation arrhythmias which has nothing whatever to do with the condition described by Mobitz (for example atrial flutter or fibrillation with complete A V block and independent A V rhythm, blocked atrial extrasystoles, series of ventricular extrasystoles, ventricular ectopic tachycardia). No. 5 of Phibbs classification would even extend the present confusion to other arrhythmias for example return extrasystoles. The term ventricular capture is quite acceptable as an alternative to "interference beats, but this does not in the least detract from the necessity of eliminating the use of "interference in the electrophysiologic sense in the context of the arrhythmia under discussion. If this phenomenon is to be given a name some term which does not give rise to confusion should be employed, such as "impulse collision or extinction through refractoriness.

The pioneers in this field, including Mobitz, to whose work in the first part of this century we owe so much for our understanding of arrhythmias has consistently used the term interference in the sense of interference of rhythms they are not to blame for the present confusion. The responsibility lies with those who, much later used the same term with an entirely different and in certain respects opposite connotation.

Atrioventricular dissociation with interference defines clearly the arrhythmia clarified by Mobitz. In order to eliminate the present confusion it may be advisable to modify slightly the definition at least temporarily into atrioventricular dissociation with interference beats. The variety of A V dissociation without interference beats may be termed simple A V dissociation. This classification, also adopted by Holzmann (1961) leaves nothing to be desired in regard to clarity.

Since Scherf was also singled out by Phibbs for attack I sent a draft of this letter to Scherf who has authorized me to state that he fully concurs with its contents.

Epilogue (prompted by the style of Phibbs Annotation). For I have been taught by one whose Dictates all Ages have revered that it is the Business of Physicians to make new Discoveries in Science or to perfect such as are already made rather than to spend his Time in censuring or depreciating others. Hippocrates *De Arte* (John Barker 1747).

Appendix

A. Eine Deutung als Interferenz trotz der gleichbleibenden Kopplungen erscheint gegeben da wir hier den Rhythmus der Tätigkeit beider Zentren direkt der Kurve ohne Rechnung entnehmen können. "Eine Dissoziation erkennen wir—und das sind die weitaus häufigsten Fälle— an der in verschiedenem Rhythmus erfolgenden voneinander unabhängigen Tätigkeit zweier Herzteile die wir direkt registrieren oder wir können sie durch genaue Analyse der unregelmässigen Schlagfolge eines Herzteiles, die wir als Interferenz mehrerer regelmässiger Rhythmen auffassen, erschliessen. Bei dieser Interferenz die wir bisher haben kennen lernen, ist der Rhythmus der wir in vereinzelten Schlägen zu Gesicht bekommen wird der langsamere Bei der Interferenzdissoziation ist dies stets der Sinusrhythmus. Er ist dem Grundrhythmus der Kurve übergeordnet und führt sobald er auf den untergeordneten Herzteil übergreift zu einer Phasenverschiebung des heterotopen Rhythmus. Eine Schutzblockierung des untergeordneten Zentrums entsteht hier lediglich durch Einlagerung während und kurz nach ihrer Erregung refraktärer Herzteile in die Bahn der Ausbreitung des Sinusreizes. Diese Art der Schutzblockierung ergibt sich daher ohne weitere Voraussetzungen aus einem allgemein anerkannten Prinzip der Herzphysiologie.

B. Im weiteren Verlauf wird mit dem immer rascher erfolgenden Sinken der Ventrikelfrequenz die Anzahl der vom Vorhof übergeleiteten Schläge immer zahlreicher es entstehen je nach der Differenz der beiden Rhythmen verschiedene Formen von Allorhythmie.

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To the Editor:

If the reader has survived Dr. Schott's "Sturm und Drang," I should like to state the facts at issue as simply as possible.

Dissociation of atrial and ventricular rhythms may be caused by one of two mechanisms: (A) block within the A-V node (meaning organic disease or toxic dysfunction of the node) or (B) the discharge of an ectopic pacemaker in the A-V node or in the ventricles. Rarely both may operate.

We use the term "trioventricular block" for dissociation of type A. Many people have used the term "interference-dissociation" for type B. (This is a good term since the dissociation is caused by the action of the ectopic pacemaker which *interferes* with the spread of the sinus impulse.) It is precise and descriptive. It tells *kind* and *cause*. It is specific.

Schott doesn't want to use the word "interference" in this sense. He doesn't want to give *any* specific name to dissociation of type B.

He wants to use the term "trioventricular dissociation" both as a *general term* for the two kinds of dissociation and as *the specific* term for type B. (One would imagine there were a word shortage.) He assumes that the clinician will be able to guess whether he is talking about trioventricular block or dissociation of type B. He doesn't say how.

Schott would like to use the word "interference" to describe *ventricular capture*. This is a relatively minor phenomenon. It takes place in some dissociations of type B but not all. It is not the cause of the arrhythmia. There is no reason to indicate it in the title of the arrhythmia.

Why does Schott insist on using the word "interference" to describe this minor variant, rather than to designate the cause of the arrhythmia?

Why doesn't he think this arrhythmia (type B) is entitled to a specific name of its own?

Schott is very inconsistent. In the final (or "Götterdämmerung") portion of his letter Schott agrees with the two points I raised. He admits that "ventricular capture" is a good term to replace his usage of "interference." He also admits that we need a word to describe the effect of an ectopic pacemaker in producing dissociation.

Hurrah! One assumes that we are now free to use the word "interference" in its proper electrophysical sense to designate the cause of the arrhythmia. But Schott says no.

He proposes instead the term "extinction through refractoriness!"

The diagnosis will now be "extinction-through-refractoriness-dissociation!"

This illustrates the grand old principle of never using *one* word if you can crowd in three. It is reminiscent of "Asphalt Deutsch," the ponderous, obscure, clumsy language used by German academicians to make simple things sound complicated.

Schott wants to know what I would call "atrial fibrillation or flutter with complete A-V block." If A-V block were actually present, I would call them "atrial fibrillation or flutter with A-V block." What's *the problem? Interference-dissociation* implies the presence of two competing pacemakers (or rhythms; the terms are usually synonymous for

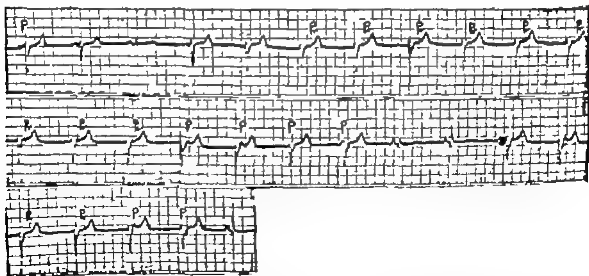


Fig. 1. This tracing illustrates the phenomena in question. An ectopic pacemaker is discharging in such a way as to interfere with the passage of most sinus impulses. *Sinoatrial capture* of the ventricular rhythm takes place in the third beat of the top strip, the eighth and ninth beats of the second strip, and the last beat on the bottom strip. *Ventricular capture* of the atrial rhythm with retrograde conduction to the atria takes place in the beats labeled *Pr*. *Interference* takes place when the sinoatrial impulse is halted by the effect of the discharge of the ectopic pacemaker in many impulses (such as those labeled *P*). If the word "interference" is used to mean capture, we *have no specific word to describe this last-named phenomenon. If the words* "capture" and "interference" are used in the separate senses indicated above, there is no linguistic problem.

practical purposes). I hope Schott is clear on that point. I assume that he is not confused by the simple interference which accompanies most atrial flutter for instance (cf. my text, *The Cardiac Arrhythmias* The C. V. Mosby Company, available in London at Henry Kimpton).

Schott appeals to "history" for support. He has curious ways with references. He quotes Wenckebach and Winterberg[1] in support of the use of "interference" to mean capture beat. As Marriott points out, these authors did not use the word in that sense. One of the tracings in their article is labeled "dissociation with interference." *There are no capture beats* in this tracing; therefore these authors didn't mean to use "interference" to designate ventricular capture. They used the word "Verkettung," or linkage. So did Mobitz, the first to coin the name "Interferenzdissoziation."

Mobitz wanted to distinguish A-V dissociation caused by an ectopic pacemaker from the kind caused by A-V block. He explains this at length. He realized that ventricular capture was an interesting but minor phenomenon which sometimes altered the rhythm of the ectopic pacemaker briefly. (He certainly didn't insert a word for this minor aberration into the title of the arrhythmia while leaving out any word for the *cause* of the arrhythmia—the thing that made it unique—the discharge of the ectopic pacemaker!)

To spare the editors and conserve journal space I will simply invite any readers who are interested to write me directly. I will be glad to quote chapter and verse on Mobitz' article as well as Schott's other references.

In brief, Scherf and Schott became so fascinated by the small bush of ventricular capture that they ignored the whole forest—the cause and essential character of the arrhythmia—the interference set up by the ectopic pacemaker.

Schott ends by proposing the name "simple atrioventricular dissociation" for dissociation of type B without ventricular capture. He might also mean complete A-V block, by his own admission. You can't tell which he means from the name. See the point.

Replying in kind to Schott's quotation from Hippocrates, I must close with this couplet freely translated from Hesiod:

> He exposes himself to derogation and even barbed witticism
> Who goes about quoting classical authority to place himself beyond the reach of criticism.

Honest Scherf and Schott need not feel guilty about their linguistic lapse. No one has died or been hurt as a result of it. Mobitz, though a good scientist, was one of the worst writers in scientific history. He could crowd six relative clauses between article and subject, and by the time the reader found the verb he felt as though he had trekked through Outer Mongolia. He was a real master of hoch-asphalt Deutsch. No wonder things became confused!

Brendan Phibbs, M.D.

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Book reviews

THE PNEUMOCONIOSES. Edited by A. J. Lanza, Director Emeritus and Professor Emeritus, Institute of Industrial Medicine, New York University. New York, 1963. Grune & Stratton, Inc. 154 pages. Price $7.50.

In this monograph pneumoconioses are defined as those pulmonary diseases which result from the inhalation of inorganic dust, are characterized by the formation of fibrous tissue in the lungs, and result from occupational exposure to these dusts. It should be recognized that this definition excludes such occupational pulmonary diseases as byssinosis and bagassosis which are due to the inhalation of organic dust. The subject matter is treated very thoroughly in this work, both from clinical and pathologic standpoint. Particularly enlightening are the sections on asbestosis, beryllosis, and coal workers' pneumoconiosis. The reproductions of chest roentgenograms are fair but the quality of the histophotography is good. A section on the medical-legal aspects of the pneumoconioses will be of particular interest to those physicians who are engaged in the evaluation of patients with this group of diseases. Emphasis is placed on the fact that functional evaluation cannot be adequately made from the chest x-ray film or the length of exposure to the dust. The value of pulmonary function studies in this regard is discussed. This monograph is lucidly written and recommended to anyone interested in occupational pulmonary diseases.

CORONARY HEART DISEASE (The Seventh Hahnemann Symposium). Edited by William Likoff, M.D. and John H. Moyer, M.D. New York, 1963. Grune & Stratton, Inc. 483 pages. Price $17.75.

The papers of this symposium are grouped under several major divisions: coronary circulation, coronary blood flow and myocardial metabolism, etiology of atherosclerosis, coronary heart disease—pathogenesis, clinical and laboratory diagnosis and treatment, and, finally, rehabilitation and prognosis.

Several essays deserve comment. There is a fine historical development of the use of the electrocardiogram in angina pectoris, and an intriguing report on caloric consumption by intestinal flora as related to dietary management. Commendable and concise reviews on the "state of the art" are found with regard to cardiac arrhythmias associated with recent myocardial infarction and the measurement and significance of serum enzymes. (Figure III in this latter essay is obviously not the one intended either by text or legend.) A delightfully written editorial deals with the anticoagulant controversy.

Unfortunately, the remainder of the book suffers from the most frequent disorder noted among published symposia: "book filler syndrome," which is manifested largely by the walk-on, cursory review of the literature by local members of the faculty or off-the-cuff pronouncements by orators who were asked to appear and repeat some of their most famous lines. There is also a possibly hazardous section on the treatment of cardiogenic shock, the format of which is a quick listing of recipes of potent drugs, with detailed and categorical dosages but scant mention of indications and circumstances of use. Any reader who needs to know the dosages needs qualifying information even more vitally. This reviewer recommends that interested physicians borrow the book for its few worth-while sections.

CURRENT THERAPY 1963. Edited by Howard F. Conn, M.D. Philadelphia, 1963. W. B. Saunders Company. 775 pages. Price $12.50.

This is the fifteenth in the annual series of this well-known book. It requires little review since the format and type of information provided are quite familiar to most physicians. The section on the cardiovascular system is well presented and fulfills most of the needs of the general practitioner and the general internist. Even the cardiologist could gain profitably from certain parts of this section although in general the information provided is not directed to his level. One area that seems to be somewhat deficient concerns the medical management of peripheral vascular diseases. Another topic of usefulness would be the management of shock presented separately with particular emphasis on the merits and indications of the various vasopressor drugs. Finally, because of its increasing importance, a section dealing specifically with the more frequent problems encountered in geriatric patients would be helpful to all.

This reviewer believes that the book fulfills a very distinct need, and that its acquisition by the practicing physician can be recommended.

PHYSICAL DIAGNOSIS OF HEART DISEASE. By Noble O. Fowler, M.D., F.A.C.P., Associate Professor of Medicine, University of Cincinnati College of Medicine. New York, 1963. The Macmillan Company. 521 pages. Price $12.50.

As the title implies, the central theme of this book concerns physical diagnosis in regard to the heart. The information provided, however, is not limited to physical findings since pertinent data gained from the history as well as from laboratory procedures, such as radiography, electrocardiography, phonocardiography, cardiac catheterization, and angiocardiography are well integrated into the discussions. The orientation of this book could best be described as cardiac diagnosis with special emphasis on the physical examination. Such an approach is a helpful one and has much appeal. One characteristic that tends to distinguish the internist from others in the

medical field is their interest in and facility with physical diagnosis. Because of this Dr Fowler book should provide enjoyable reading for this group.

Most cardiologists who read this book will have the feeling that they could have written certain sections in more detail and with more profit to the reader while still respecting the limitations of avoiding excessive length or controversial issues. Concerning many minor points the cardiologist will find himself disagreeing with Dr Fowler to a large or small extent. As is common in first editions several minor errors are evident. One electrocardiogram appears to be mounted upside down.

Such flaws, however are really insignificant. This is an excellent book. The contents are informative, and the style of writing is clear and interesting. The paper print, and illustrations are of high quality. Indexing is adequate.

This book can be recommended wholeheartedly. It should manifest its greatest worth to those in the fields of internal medicine and pediatrics. It is not intended for the experienced cardiologist.

A Primer of Cardiology. By George E. Burch M.D. Third Edition, Philadelphia 1963 Lea & Febiger 366 pages. Price $6.

This volume is aimed at beginners in cardiology whether they be students or physicians. It is intended to show how basic physiologic and hemodynamic phenomena are expressed in normal man and modified by heart disease.

The purpose of the book, as indicated by this quotation from the preface, has been well achieved. The arrangement consists of a chapter which deals with the anatomic considerations followed by one entitled Approach to the Diagnosis of Heart Disease. This second chapter contains a great deal of practical clinical information and in addition, a scholarly discussion of many of the important physiologic and pathophysiologic concepts of heart disease.

The third chapter which is entitled The Approach to Clinical Examination, deals largely with methods of examination and the interpretation of the findings. Much of the chapter is concerned with auscultation heart sounds and heart murmurs. Here again the principles involved are well woven into the discussion of the practical implications of auscultatory phenomena. It seems to this reviewer that the discussion of the history is somewhat too brief in relation to the importance of the subject. Thus, auscultation occupies almost 80 pages, whereas the history takes only about 4.

The fourth major area of the book is devoted to etiological considerations of the common types of heart disease. This chapter ends with brief discussions of the treatment of congestive heart failure, of angina pectoris, and of myocardial infarction.

The fifth and final chapter is entitled, Bedside Diagnosis of Cardiac Irregularities. In view of the frequency of these disorders and their responsiveness to treatment, the amount of space devoted to them is not disproportionate to their importance.

Although Dr Burch is one of the authorities in the field of electrocardiography he has deliberately omitted any detailed discussion of this subject from the present volume. In the opinion of the reviewer this was a wise decision, because a comprehensive discussion of electrocardiography would tend to take the reader's mind away from those concepts of integration of pathophysiology and clinical medicine which appear to be the chief object of the book.

The term primer as used in the title of the volume should not be confused with superficiality. In the consideration of hemodynamic phenomena and of pathologic physiology the volume has considerable profundity and even the experienced clinical cardiologist or the experienced investigator in the field will have ample to learn by reading the discussions. The fact that other investigators may not agree with all of the author's concepts does not reflect adversely on the volume. The reader properly expects the author to express his own points of view about controversial and unsettled questions.

The critical reader will find many statements with which he is in partial agreement only. Thus, the statement (page 42) that "heart block, regardless of the type or degree is a definite sign of heart disease, would indicate that a healthy athlete with sinus bradycardia and a P R interval of 0.23 second was suffering from cardiac disease, even though the administration of atropine promptly caused the P R interval to shorten to less than 0.20 second. Similarly many readers would disagree with the conclusion (page 51) that anemia with less than 50 per cent circulating hemoglobin of several weeks duration indicates heart disease. The reader may be inclined to think of severe anemia as a clear indication of increased load on the heart rather than a necessary and absolute sign of cardiac disease. However considerations of this type are largely semantic rather than conceptual in nature. In any book which attempts to cover a complex subject in brief space (and it may be stated that this one does so with great success) it is not possible for the author to express all of the qualifications exceptions, etc. which could be appropriate to a more lengthy treatise. To condemn a first-class intellectual achievement because of such minor oversimplifications is to fall into the common trap of believing that the function of a reviewer is to emphasize picayunish criticism at the expense of objective evaluation.

All books have virtues and defects. This one possesses the great virtues of brevity, clarity and simplicity combined with a considerable degree of profundity. The ratio of virtues to defects, which should be the guide to the value of any scientific work is very high. Not only the beginners, to whom the book is primarily directed, but also the experienced clinician and the investigator will find this volume valuable

Announcements

A GRADUATE COURSE IN MEDICAL HYPNOSIS is being offered to physicians and dentists by the University of Pennsylvania Grad te School of Medicine The Department of Neurology nd Psychiatry is in charge of organizing the sessions.

There will be 24 weekly afternoon sessions for *total of 96 hours, beginning Oct. 2 1963*

The course will be given t the Institute of the Pennsylvania Hospital 111 North 49th St. Philadelphia 39 Pa

The teaching staff of eight is headed by Lauren H Smith M D Professor and Chairma of Psychiatry Department of Neurology and Psychiatry t the Graduate School of Medicine. Dr Smith is Consultant for Medical Development of the Instit tut of the Pennsylvania Hospital. The taff will include Dr Harold Rosen head of th America Medical Association Committee on Hypnosis.

A symposium on SUDDEN CARDIAC DEATH will be held t the University of Kentucky Medical Center Lexington, Ky on Oct. 4 and 5 1963 The participants will include the following *Guest Faculty*—Samuel Bellet, M D Philadelphia Pa Baruch Bromberger Barnea, Ph D Baltimore, Md Leonard S Dreifus, M D Philadelphia, Pa. A. Sidney Harris, Ph D New Orleans, La. Herman K. Hellerstein M D Cleveland Ohio Brian F Hoffman, M D Brooklyn N Y Richard Langendorf M D Chicago, Ill. Eugene Lepeschkin, M D Burlington, Vt. Gordon K. Moe, M.D Utica, N Y Alfred Pick M D Chicago Ill. Richard S Ross, M D Baltimore, Md. Da[illegible] Scherf M D New York, N Y David M. Spain, M.D Brooklyn, N Y Demetrio Sodi Pallares, M D Mexico City Mexico Paul M Zoll, M D Boston, Mass. *U versity of Kentucky Faculty*—Peter Bosomworth M D Dept. of Anesthesiology Alberto Mazzoleni M D Dept. of Medicine Edmund D Pellegrino M D Dept. of Medicine Frank C. Spencer M D Dept. of Surgery Borys Surawicz, M D Dept. of Medicine.

All pplicants should register i advance. The registration fee is $20 (not required of members of the Kentucky Heart Association, house officers, research fellows, graduate students members of the armed forces, and f ll-time teachers in the medical schools). Checks should be made payable to the University of Kentucky and should be sent with completed pplication form t Dr Borys Surawicz, Dept. of Medicine Uni ersity of Kentucky College of Medicine, Medical Center Lexington, Ky

The THIRD INTERNATIONAL CONGRESS OF CYBERNETIC MEDICINE, promoted and organized by the International Society of Cybernetic Medicine, will be held in Naples, Italy March 21 24 1964 under the Presidency of Professor Aldo Masturzo.

Scientific works will concern the following subjects *biocybernetics neurophysiology; automatic* calculation applied t biological research cybernetics of rheumatic osteoarticular diseases cybernetics of cancer cybernetics pplied t space medicine all subjects related t cybernetics pplied to medicine and biology

The official languages of the Congress will be Italian, English French, German, and Russian.

Excursions, entertainment, and a post-Congress tour will be organized.

The subscription fee is $20 for active members, and $12 for inactiv members. Payment of the fees entitles members to ttend all events, except the post-Congress tour

All correspondence in regard to the scientific program and general information should be addressed to Secrétariat d Congrès, Société I ternationale de Médecine Cybernétique, 348, Via Roma, N ples, Italy

A course in INTERPRETATION OF COMPLEX ARRHYTHMIAS will be given at Michael Reese Hospital nd Medical Center by Louis N Katz, M D Richard Langendorf M D and Alfred Pick, M D This is an *advanced* course intended for experienced electrocardiographers The class will meet daily from 9.00 A.M. to 5:00 P.M., Dec. 2 7 1963 Registration is limited to 30

Further information and a copy of the lecture schedule may be obtained from Miss Donna Adler Office of Medical Education, Michael Reese Hospital nd Medical Center Chicago 16, Ill.

THE THIRD ASIAN PACIFIC CONGRESS OF CARDIOLOGY and THE TWENTY EIGHTH ANNUAL MEETING OF THE JAPANESE CIRCULATION SOCIETY will be held in Kyoto, J pan, May 10 through 14 1964

Address correspondence t : Maekawa Magojiro, President, Asian-Pacific Society of Cardiology The Third Medical Clinic, Kyoto Uni ersity Hospital Sakyo-ku Kyoto, J pan.

American Heart Journal

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Editorial

Extremes of coronary heart disease mortality in ethnic groups in Johannesburg, South Africa

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Johannesburg South Africa

Among white populations it is well known that there are wide differences in mortality from coronary heart disease (CHD) in countries on the same continent (England Switzerland) in different regions of the same country (Finland[1] United States[2]) in adjacent states of the same country (United States) and in constituent populations in the same section of a city (Manhattan[5]) It is also known that differences in mortality are still more divergent where there are multiracial populations in the same city (Chicago Singapore[7]) Perhaps the greatest contrast of all is found in Johannesburg where mortality from CHD among the Jewish portion of the white population is extremely high yet where mortality among the African Bantu is very low Neither of these extremes of mortality can be wholly accounted for

It is not exceptional of course for a particular disease or abnormal condition to occur excessively yet for the cause to be partly or even wholly unknown Thus there is the high incidence of cholecystitis among the Pima Indians in Arizona vesical stone in the young in parts of India hypertension and hypertensive heart disease in Negroes in the United States, and cryptogenic heart disease (formerly called nutritional heart disease) among the South African Bantu[11] Among the total white population of South Africa the CHD mortality rate up to 50 years of age is higher than that of the United States.[12] In Johannesburg (400 000 whites) the proportions of deaths due to CHD among whites in the different age groups are higher than such deaths among South African whites as a whole[13] in this same city the proportion of such deaths among the Jews (40 000) is almost *double* that among the non Jewish white population Briefly in 1960 among Jewish males who were 45 to 74 years old there were 176 deaths, of which 86 i.e. 49 per cent were certified as being due to CHD among the non Jews, there were 1 033 deaths, of which 288 i.e. 28 per cent were due to the disease For Jewish females, the corresponding proportion who died from CHD was 58 out of 140 i.e. 41 per cent and for non Jewish females, 129 out of 653 i.e. 20 per cent. Thus, every second death among Jewish middle-aged and elderly men was due to CHD Furthermore it will be noted that the percentage mortality from CHD among *Jewish females* namely 41 per cent, was much higher than that among

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Address South African Institute for Medical Research, P O Box 1038, Johannesburg South Africa.

non Jewish males namely 28 per cent. In regard to Jews elsewhere it is known that among those in New York the mortality from CHD is higher than that among Italians.[1] In Israel although the present mortality due to CHD is not outstandingly high the rate has *doubled* in the last 10 years thereby contrasting with that due to cancer and cerebral vascular disease (CVD) which are other leading causes of death whose rates have remained steady.[3] Incidentally in respect of CVD mortality examination of local data has shown that there is no disparity between the Jewish and non Jewish moieties. It would probably be true to say and this is undoubtedly of major significance that the Jewish community as a whole in Johannesburg enjoys a higher standard of living than any other equally large group of Jews extant. In so far as diet is implicated it is likely that the fat ingested provides a somewhat higher proportion of calories than does the diet of other Johannesburg whites. For the Jewish people the parameters of hypertension obesity activity stress and smoking are not known with certainty however the impression of clinicians is that hypertension overweight and physical inactivity and perhaps business stress, are more pronounced in middle-aged Jews than in middle-aged non Jews. Biochemically the mean level of serum cholesterol in a group of middle aged Jewish adults was found to be only slightly higher (245 mg per cent) than the corresponding mean found for non Jewish whites (235 mg per cent). No comparative studies have been undertaken on the grading of atherosclerotic lesions in the aorta and coronary vessels in the two groups. In the light of our present knowledge the differences known or suspected to prevail between Jews and non Jewish whites in Johannesburg seem to be insufficient to account for the fact that the CHD mortality of the former is almost double that of the latter.

Among the local Bantu it is indisputable that death from myocardial infarction very rare. Evidence is based primarily on the results of thousands of postmortem examinations carried out by many pathologists at several centers and also the examination of electrocardiographic tracings undertaken on several hundred of adults in various places. Almost uniformly the findings have been negative.[14] Thus among an urban population of about 600 000 Bantu in Johannesburg of whom at least 10 000 are over 65 years of age it is doubted whether there are more than say 10 deaths *per annum* from CHD. In endeavors to learn to what extent the more westernized Bantu are becoming more prone to die from CHD studies are being undertaken on (1) elderly Bantu servants in rich white households (2) elderly Bantu school teachers with much more means and culture than the masses, and (3) Bantu who have been diabetic for at least 5 years. Studies undertaken up to the present have not been revealing thus although diabetes is more than half as common in urban Bantu as in whites only 4 Bantu diabetics are known to have died from CHD within the last few years.[7] Nevertheless, whereas the great majority of Bantu are habituated to a frugal diet and unsophisticated manner of life we know that there is a proportion admittedly small who are accustomed to a diet of higher energy value and fat protein contents who have relatively high levels of serum cholesterol long clot lysis times, and occasionally severe atherosclerosis. There are some too who have hypertension obesity and sedentary jobs with increasing responsibility some are given to increased smoking. Moreover at the altitude of Johannesburg (6 000 feet) there are many who have hematocrits above 50 per cent and hence presumably have disproportionately heightened blood viscosity.[1] Yet the existence of all these factors is consistent with this very low incidence of acute coronary episodes. Bearing in mind the increase of CHD among Japanese in California[18] Yemenites in Israel[19] and other similar populations in transition then surely there ought to be a well discernible progressively increasing frequency of deaths from CHD among Bantu since many have been exposed for decades to urbanization with all its concomitant changes.[20]

We cannot as yet weigh the relative influence of predisposing and of precipitating factors in CHD nor can we be sure that these factors exert equal influence in populations which differ in race environ

ment, and culture But clearly there are factors, whose weight is not sufficiently appreciated which are promoting excessive CHD mortality in the case of the Jews conversely there are different factors which are retarding CHD mortality among urban Bantu. In South Africa there is also excessive mortality from CHD among Indians,[illegible], [21] whose unusual proneness to the disease is also not readily explicable and among whom, in Durban over a quarter of the fatal attacks occur before 45 years of age. In contrast there is retardation of the disease in another African group the Samburu[22] a milk-drinking nomadic population whose intake of fat for part of the year exceeds that in the United States.

These anomalies of mortality from coronary heart disease caution still further against attaching excessive blame to any one etiological factor and also against being too sanguine over the ameliorative effect on coronary heart disease of reducing the concentration of serum cholesterol by therapeutic means.

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Clinical communications

Angina pectoris with coexisting skeletal chest pain

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There are many excellent reports describing innocent causes of chest pain which may be confused with ischemic heart disease.[1-4] However, the frequent coexistence of angina pectoris with skeletal chest pain has not been sufficiently emphasized. In 1928 Eckerson and associates reported on 4 patients who, after a myocardial infarction, had persistent discomfort in the anterior chest not due to further myocardial ischemia. They attributed the pain to the presence of the myocardial scar. Musculoskeletal chest pain after myocardial infarction was found in 13 per cent of 60 patients studied by Edwards. In many of these patients the innocent disorder was confused with myocardial ischemia or necrosis. Others[1] have been impressed with the frequency of complaints of pain in the anterior chest wall after myocardial infarction for a period of time up to 9 to 12 months. The present report indicates that a similar pain often exists in patients with angina pectoris who have no evidence of myocardial infarction.

This study was undertaken to test the validity of our clinical impression that skeletal chest pain is more common in patients with angina pectoris than in individuals of the same age decade and sex who have no heart disease, and to suggest a diagnostic approach to these often difficult patients.

Plan of study

The records of 2,213 referred medical patients were reviewed. Three hundred and three patients presented convincing evidence of angina pectoris. Three hundred and three control subjects were selected at random, except that the absence of any clinical evidence of heart disease was stipulated, and these were paired by age decade and sex with the patients of the angina pectoris group. The incidence of anterior chest pain of skeletal origin was determined for both groups.

Angina pectoris group. A diagnosis of angina pectoris was made in 303 patients. Inclusion in this group was based on one or more of the following criteria, in addition to whether the history was typical or atypical.

1. POSITIVE ELECTROCARDIOGRAPHIC EXERCISE TEST. This is defined as a postexertional depression of the entire S-T segment below the base line (P-R segment) of at least 1 mm. in any lead and having either a horizontal or sagging configuration. A depressed S-T junction which rose acutely into a T wave was not regarded as an indication of myocardial ischemia. Arrhythmias, conduction defects, and isolated T wave changes alone after exercise were not considered to constitute a positive test.

In patients who were taking digitalis, electrocardiographic changes after exercise

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were not used as a criterion for the diagnosis of angina pectoris.

2 PROMPT AND COMPLETE RELIEF OF PAIN BY NITROGLYCERIN *Prompt* is defined as within 10 minutes, and the word *complete* emphasizes that many patients with skeletal pain frequently state that they obtain some degree of relief but not *complete* relief as is seen in most instances of angina pectoris.

3 CONSISTENT INCREASE IN THE AMOUNT OF EXERCISE REQUIRED TO INDUCE CHEST DISCOMFORT AFTER NITROGLYCERIN AS COMPARED WITH A PLACEBO CONTROL. When chest discomfort came on during exercise the test was stopped immediately The duration of exercise and the number of ascents required to precipitate pain were noted The same rate of exercise was repeated after a placebo (saccharin tablet) and finally nitroglycerin the patient rested 45 minutes between each exercise attempt These tests were repeated several times on separate days under conditions which were similar as regards relationship to meals emotional stress, and environmental temperature

To satisfy this criterion the amount of exercise required to induce chest discomfort must be consistently increased approximately 50 per cent or more after nitroglycerin with little or no increase after a placebo.

Control group Three hundred and three control subjects were selected at random except that the absence of any clinical evidence of heart disease was stipulated. All had normal resting electrocardiograms, and the majority were exercised to their physical tolerance and exhibited a normal postexertional tracing In all patients who had a history of chest pain negative results were demonstrated by all of the objective criteria listed for the angina pectoris group. Subjects from the control group who showed any of the following questionable changes in their postexertional electrocardiograms were excluded (1) depression of the entire S-T segment below the base line (P R segment) of 0.5 minute or more with a horizontal or sagging contour (S-T segment depressions of 0.5 mm. to less than 1 mm. were regarded as borderline) (2) arrhythmias, including ventricular nodal or atrial premature contractions (3) transient conduction defects (4) T wave inversions.

Patients with benign arrhythmias or a history of palpitation were also omitted from this study

Patients were excluded from both groups when any one of the following conditions existed (1) shoulder-hand syndrome (2) valvular or congenital heart disease (3) hiatal hernia peptic ulcer or gall-bladder disease (4) history or clinical evidence of syphilis (5) myocardial infarction without angina pectoris.

Criteria for the presence of skeletal chest pain The diagnosis of skeletal chest pain was made when a patient presented with a complaint of pain having the following characteristics (1) Long duration i.e several weeks or more (as opposed to acute skeletal chest pain which sometimes follows some recent unusual effort or strain) (2) Described as a soreness, aching tenderness, sharp knifelike, or sometimes as tightness. (3) Intensity commonly minimal to moderate but occasionally severe. (4) Usually felt over the precordium, beneath the sternum at the xiphoid or at the chondrosternal or costochondral junctions. (5) At times well localized to a small area but usually diffuse. (6) Occasionally radiates into left arm. (7) Onset usually very gradual over many minutes, but at times practically instantaneous in that the maximal intensity is reached almost with the first sensation of discomfort. (8) Lasting seconds or hours (but not for a few minutes only) (9) Intensity usually waxes and wanes with specific body movements but may be constant. (10) Not usually precipitated by factors that increase cardiac work such as exercise emotional stress, and the postprandial state. (11) Not promptly and completely relieved by nitroglycerin. (12) Often associated with local tenderness. (13) Favorably affected by salicylates, warmth local injections of procaine and sometimes by steroidal hormones.

Results

Of the 303 patients with angina pectoris 155 (51 per cent) had clinical evidence of anterior skeletal chest pain whereas in the 303 control subjects, only 70 (23 per cent) exhibited this disorder (Table I) These

Table I

Age	*Number each group (anginal and control)*	*Anginal group (number with skeletal pain)*	*Control group (number with skeletal pain)*
20–29	1	1	1
30–39	13	8	5
40–49	55	30	10
50–59	120	58	36
60–69	93	46	16
70–79	19	10	2
80–90	2	2	0
Totals	303	155 (51%)	70 (23%)

data were analyzed by the chi square technique and were found to be highly significant ($p < .001$).

The records of 150 of the 155 patients with both angina pectoris and anterior skeletal chest pain afforded reasonably certain evidence whether a prior myocardial infarction had occurred. Seventy-nine (53 per cent) of these 150 patients had no evidence of myocardial infarction.

Discussion

These findings demonstrate that (at least in this series of patients) anterior skeletal chest pain is more common in patients with angina pectoris than in individuals of the same age decade and sex with healthy hearts. It was also found that skeletal chest pain often exists in patients with angina pectoris in the absence of evidence of myocardial infarction.

It is likely that the incidence of chest wall pain found in the control subjects (23 per cent) is higher than in the comparable general population. All of these patients were referred by physicians and in many instances the chest pain constituted the chief reason for such referral. This circumstance would tend to further increase the marked difference already noted in the incidence of skeletal chest pain in the two groups.

The skeletal chest pain reported here seems to be analogous to that of the shoulder-hand syndrome although less dramatic and without local swelling or involvement of the shoulders and hands. Presumably a similar mechanism exists for both conditions. Skeletal chest pain may exist with the shoulder-hand syndrome, but patients who had involvement of the shoulders or hands were excluded from this study. Although the two conditions present entirely different clinical pictures, it is of interest that both have occasionally responded at times dramatically to oral cortisone therapy.

Certain conditions, such as distention of abdominal viscera, are known to cause reflex constriction of the coronary arteries but this probably never induces anginal pain in normal subjects.[1] In some patients with coronary atherosclerosis, however, skeletal chest pain can apparently precipitate anginal attacks. We have observed several patients with typical angina pectoris whose pain and electrocardiographic changes could be produced by the skeletal chest pain acting as a trigger. The following case history illustrates this phenomenon.

Patient B. K. This 54-year-old white woman had had her first episode of chest pain 3 years prior to hospitalization. While planting flowers, she was seized with a severe vise-like substernal constriction which radiated into both arms and hands and the anterior neck. A few minutes later she became unconscious. A myocardial infarction was documented. In the subsequent 2 years, she sustained two other myocardial infarctions at approximately yearly intervals. For 2½ years she had also had typical anginal pain. Walking precipitated the discomfort only if undertaken within 2 to 2½ hours after a meal, whereas excitement or anger readily induced pain. An identical discomfort would always follow the brushing of her teeth, bending forward, and certain specific movements of the arms such as raising both arms above her head or reaching for an object on a high shelf. Nitroglycerin would consistently relieve the pain completely within 5 minutes. The patient was not aware of any other type of chest discomfort.

Gall-bladder and gastrointestinal x-ray films were normal. Physical examination revealed a small pre-

cordial lift[12] and Grade 1 short, late systolic apical murmur.

A resting electrocardiogram showed abnormal Q waves in Leads II, III, and aVF with normal S-T segments and T waves in all 12 leads.

When seen at the time of ward rest on the following day, she exclaimed that she had just finished brushing her teeth and was having an episode of chest pain. Examination revealed marked visible, as well as palpable, precordial lift, and during the pain the previously described Grade 1 murmur was of Grade 4 intensity. After nitroglycerin the pain promptly subsided. The precordial lift was no longer visible and was barely palpable. The Grade 4 murmur returned to Grade 1 intensity.

Several subsequent examinations revealed that the motion of her right arm as used in brushing her teeth, would regularly induce anginal pain and the above-described physical findings, together with marked depression and sagging of the S-T segments in the electrocardiogram. It was found that firm pressure upon the third left chondrosternal junction would regularly induce anginal pain, with the attendant changes, whereas pain to the point of weeping, by pressure on the Achilles tendon and fingernail, would cause none of the above-mentioned reactions. After procaine anesthetization of this tender area, neither the application of firm pressure nor any arm movement resulted in anginal pain.

The obvious conclusion drawn from these observations is that the skeletal tissues were capable of initiating reflex coronary constriction and anginal attacks in this patient with advanced coronary artery disease. A similar patient has been reported on by Reeves and Harrison. During an attack of anginal pain a precordial lift resulting from local ballooning of ischemic muscle may be identified occasionally in patients by special techniques, such as the kinetocardiogram and by palpation in a somewhat lesser number. We have on rare occasions detected for the first time a short late apical systolic murmur in patients during anginal pain. Presumably this finding is due to distortion of papillary muscles as the result of focal myocardial ischemia.

Anginal pain and characteristic electrocardiographic changes have occasionally been noted in our own patients with angina pectoris and a coexisting hiatal hernia by distention of the stomach with air. Presumably these phenomena are caused by reflex coronary constriction.

In any patient with a complaint of chest pain it is important to first exclude angina pectoris beyond any reasonable doubt before other causes of the discomfort are sought. The presence of ischemic heart disease can usually be determined by a careful history when the complaints are typical. Skeletal chest pain which coexists with angina pectoris frequently modifies the symptoms of both disorders, so that an extremely puzzling situation results. In a considerable fraction of our own patients with both angina pectoris and skeletal chest pain, the more important ischemic pain was confused with or even masked by the coexistence of the innocent disorder.

There is sound experimental evidence for the view that visceral pain and deep skeletal pain are mediated through a common deep sensory system.[12] It is not surprising that their characteristics should be similar and that, on occasion, differentiation between the two may be extremely difficult. The importance of a careful and thorough history in evaluating any chest pain cannot be overemphasized.

When the history is inconclusive, evaluation of the postexertional electrocardiogram and observation of the effect of nitroglycerin on the response to exercise discussed earlier will frequently be of crucial diagnostic value in determining whether angina pectoris exists. The reader is referred to the excellent papers of Wood,[13] Scherf,[14] and Lepeschkin[15] for further details of the electrocardiographic exercise test.

In the patient with atypical or puzzling chest pain, usually due to the coexistence of skeletal chest pain with angina pectoris, we believe that this approach offers a means whereby a reasonably certain answer can be obtained and thus will frequently enable the physician to find the anginal "needle" in the "haystack" of skeletal chest pain.

The results reported here indicate that skeletal chest pain is more common in patients with angina pectoris than in individuals of the same age decade and sex with healthy hearts. Therefore it is important to institute a meticulous search for angina pectoris in any patient presenting with obvious chronic skeletal chest pain.

Summary

The records of 2,213 referred medical patients were reviewed. Three hundred and

three patients presented convincing clinical evidence of angina pectoris. An equal number of control subjects was randomly chosen on the basis of an absence of any cardiac disorder and were paired as to age decade and sex with the patients of the angina pectoris group. The incidence of anterior skeletal chest pain was determined for both groups.

Clinical evidence of anterior chest pain of skeletal origin was present in 51 per cent of the patients with angina pectoris and 23 per cent of the control subjects. This represents a significant difference by chi square analysis ($p < .001$).

In patients with angina pectoris, skeletal chest pain frequently occurs in the absence of a prior myocardial infarction. In some patients with angina pectoris and coexisting skeletal pain, the skeletal disorder may precipitate attacks of anginal pain. A case history which demonstrates this phenomenon of "reflex angina" is presented.

In a considerable fraction of the patients with angina pectoris the more important ischemic pain was confused with or even masked by the coexistence of the innocent disorder.

Evidence is presented that skeletal chest pain is more common in patients with angina pectoris than in individuals of the same age decade and sex with healthy hearts. Therefore, it is important to institute a meticulous search for ischemic heart disease in any patient who presents with obvious skeletal chest pain.

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Myocardial abscesses

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Myocardial abscesses have been noted in 1.52 per cent of our adult patients at autopsy during the past years. This figure represents approximately three times the highest incidence previously reported. It appears paradoxical that lesions of such frequency are sparsely discussed in the literature and go almost unmentioned in textbooks.[2] During the last 30 years, only three large autopsy series which include less than one hundred cases have been reported.[1-4] In addition, several isolated reports dealing with limited facets of the problem have been published.[11] Clinical commentary has been sparse because myocardial abscesses are usually silent and their presence is usually obscured by an associated overwhelming generalized sepsis. A survey of our autopsy protocols disclosed an increase in incidence of myocardial abscesses beginning in 1955, as well as differences in underlying disease mechanisms and etiological agents from those previously reported. To evaluate the problem in perspective, we have reviewed all our autopsies for the past 21 years.

Method of study. The cardiac findings in all autopsy protocols from 1941 to 1961 inclusive were reviewed for abscesses, suppurative myocarditis, septic embolus, infected infarcts, and bacterial endocarditis. No cases were found in children under 17 years of age. Twenty-three cases of myocardial abscesses were confirmed among 2,897 autopsies of adults. Gross specimens and photographs were reviewed when available. An average of four slides from the heart in each case were available for review. Brown-Brenn bacterial stains were prepared for each case. Clinical and laboratory data were tabulated from the records in all cases of myocardial abscesses. Histologic data were evaluated directly from the slides.

Results

Incidence. From 1940 until 1954, 4 cases of myocardial abscess were noted among 1,646 autopsies (0.24 per cent). A sharp increase in incidence was noted in 1955. During the 7 years between 1955 and 1961, 19 cases were encountered among 1,251 autopsies (1.52 per cent). Table I summarizes available data on the incidence of myocardial abscesses from the three largest series previously reported. Neither this nor subsequent comparisons of our data with series from the literature imply homogeneity of the data tabulated. We are aware of differences in the number of cases stud

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ied in the degrees of thoroughness of study in the underlying disease processes leading to pyemia in the types of therapy utilized and in the chronologic periods surveyed

Sex and age incidence Seventeen patients were females and 6 were males. The youngest patient was 17 years old and the oldest was 82 Table II shows data on the sex and age incidence from this series.

Electrocardiographic studies Eighteen of our 23 patients had interpretable electrocardiograms recorded on one or more occasions. Nine had electrocardiograms taken during the last week of life 8 of these had had previous electrocardiograms available for comparison of changes.

In the entire group of 18 only one patient had a completely normal electrocardiogram All of the 9 patients who had electrocardiograms recorded during the last week of life had abnormalities among this group only 2 had previous electrocardiograms which were normal

The types and frequency of abnormalities are presented in Table III

Only 3 patients had a significant S-T segment abnormality None of these could be attributed to myocardial abscesses since one patient was on digitalis and the other 2 patients had S-T segment abnormalities for a prolonged period of time prior to death



Fig 2 Septic emboli with clusters of cocci in small vessels adjacent to otherwise normal myocardial fibers. This is the most common pathogenetic mechanism involved in the production of myocardial abscesses. Hematoxylin and eosin stain ×250.



Fig 1 Abscess of moderate size with central liquefaction necrosis The very dark clusters are bacterial colonies. Hematoxylin and eosin stain ×25

Morphologic features Abscesses were almost always multiple within the heart From one to eighteen slides (average of four) were available per heart and revealed from one to nineteen abscesses per slide (average of four) per slide. As few as two and as many as forty five abscesses (average of sixteen) were observed per patient. Since the average section measures only 1.5 cm.² by 5 micra in thickness, the number of microabscesses present in some hearts may reach several thousands.

The left ventricle which includes the largest muscle mass of any chamber was involved in each of the 23 patients. Isolated examples of involvement of all other chambers were noted but the available material precludes a precise evaluation of distribution of lesions.

Most of the abscesses were minute. In 11 cases they did not exceed 1 *mm* in greatest dimension Approximately three

quarters of the patients had lesions which were discernible grossly as minute yellow flecks, usually surrounded by a zone of hemorrhage. Only in 4 cases did the abscesses exceed 6 mm. in size. In 15 hearts abscesses extended to the epicardial surface but rupture into the pericardial space, with purulent pericarditis was not seen in this series. Perforation of the heart through a large myocardial abscess followed by hemopericardium and pericardial tamponade occurred once. In one case subacute bacterial endocarditis was the initiating lesion. Six cases occurred in association with acute bacterial endocarditis. In 5 of these 6 a primary extracardiac source of sepsis was found in the sixth the acute endocarditis followed mitral commissurotomy which was performed several days before death. None of the cases in this series were associated with an acute myocardial infarct.

The morphologic features are illustrated in Figs. 1 and 2.

Associated abscesses Abscesses were found only in the heart in 2 patients. In 21 patients, disseminated abscesses were present. Abscesses were noted in the kidneys of 14 patients in the lungs of 9 in the brain of 7 in the liver of 5 in the adrenal of 4 in the mesentery of 2 and in the thyroid of 1 patient.

Basic disease processes underlying myocardial abscesses Table II summarizes the broad range of clinical phenomena which preceded the development of myocardial abscesses in our series. Noteworthy is the rarity of preceding subacute bacterial endocarditis and the absence of osteomyelitis. The occurrence of pyemia is apparently the common denominator of this otherwise broad spectrum of disease processes.

Relation of surgical procedures to development of pyemia. In 11 of the 23 patients a surgical procedure was performed during the last month of life. The operative procedures are cited in Table II In one patient a major sepsis (an appendiceal rupture with periappendiceal abscess) existed prior to operation, but in the other 10 patients an evaluation of the clinical record strongly suggests that the surgical procedure was responsible for inducing or disseminating the pyemic process.

Postmortem bacteriology Cultures of the blood and the heart lesions were made in all but 2 patients and the results are presented in Table II Hemolytic *Staphylococcus aureus* coagulase positive was encountered in 14 patients and *Escherichia coli* was encountered in 13 patients. Eight had both of these organisms Four patients yielded other organisms or no growth. In 2 patients culture was inadvertently omitted.

Two patients with leukemia had disseminated mycotic abscesses these cases are reported in detail elsewhere. In one case the heart tissue contained only Candida whereas the other yielded Candida, Aspergillus and a mixed bacterial flora.

Table I Comparative incidence of myocardial abscess

Time period	*Number of autopsies*	*Number with myocardial abscesses*	*Per cent of myocardial abscesses*	*Hospital*	*Author*
Prior to 1937	N.S.	31	N.S.	Boston City	Weiss and Wilkins[4]
Prior to 1940	5 676	32	0.56	Michael Reese, Chicago	Saphir[6]
1929-1942	14 160	29	0.20	Cook County Chicago	Flaxman[7]
1940-1954	1 646	4	0.24	Mount Sinai, Chicago	This report
1955-1961	1 [illegible]51	19	1.52	Mount Sinai, Chicago	This report

Table II. Composite case data

Case number	Year of death	Age, sex	Basic disease process	Surgical procedure	Organism cultured	Antibiotic
1	1941	23, F	Subacute bacterial endocarditis	None	Streptococcus viridans Escherichia coli	Sulfadiazine
2	1944	50, F	Thrombophlebitis of leg vein after sclerosing injection. Acute bacterial endocarditis	Sclerosing injection into leg vein	Staphylococcus aureus	Sulfadiazine
3	1947	70, F	Thrombophlebitis of leg vein	None	No growth	Penicillin Streptomycin Sulfadiazine
4	1951	59, M	Emphysema. Bronchiectasis. Chronic pulmonary suppuration. Acute bacterial endocarditis	None	Staphylococcus aureus Escherichia coli	Penicillin Terramycin Chloromycetin
5	1955	76, F	Fracture of femur. Decubitus ulcer. Acute bacterial endocarditis	Smith-Peterson femoral nailing	Staphylococcus aureus Escherichia coli	Penicillin Dicrysticin Achromycin Terramycin
6	1955	77, F	Appendiceal perforation. Mesenteric abscess. Portal vein thrombosis	Laparotomy only	Escherichia coli Staphylococcus aureus	Dicrysticin Streptomycin Achromycin Sulfasuxidine
7	1955	82, F	Subacute enterocolitis after resection of bowel for mesenteric thrombosis. Pyemia. Terminal cerebral hemorrhage	None	Escherichia coli	None
8	1956	47, F	Adenocarcinoma of cecum with metastases. Pyemia.	Colectomy	No culture	Sulfasuxidine
9	1956	17, M	Reticulum cell sarcoma. Pyemia	None	No culture	Penicillin Achromycin Gantrisin
10	1957	33, F	Laceration of bowel during hysterectomy	Hysterectomy	Staphylococcus aureus Escherichia coli Klebsiella Proteus Clostridium	Dicrysticin Combiotic Achromycin Chloromycetin
11	1958	62, F	Carcinoma of breast with metastases. Bronchopneumonia. Pyemia	None	Staphylococcus aureus	Penicillin Chloromycetin
12	1958	57, F	Abdominoperineal resection for carcinoma. Peritonitis. Pyemia	Abdominoperineal resection	Escherichia coli Staphylococcus aureus	Streptomycin Achromycin Chloromycetin Sulfadiazine Neomycin
13	1958	76, F	Gastric ulcer. Massive gastric hemorrhage. Infection of leg vein at cut-down site. Pyemia. Acute bacterial endocarditis	Leg cut-down	Escherichia coli Staphylococcus aureus	Penicillin
14	1959	79, M	Acute suppurative cholecystitis with pyemia	None	Escherichia coli Staphylococcus aureus	Penicillin Streptomycin Achromycin Erythromycin Chloromycetin
15	1959	38, F	Pyemia after resection of bowel for regional enterocolitis	Bowel resection and anastomosis	Staphylococcus aureus	None

Table II is continued on page 305

Drug therapy. Bactericidal or bacteriostatic drugs were administered to 19 patients. 4 received no such drugs. Nitrogen mustard was administered to 3 patients. Six-mercaptopurine was administered to one patient. Only 4 patients received steroids for periods longer than 4 days (usually in excess of 1 week) in the immediate preterminal period. Steroids had not been used prior to the preterminal period in any of these patients.

Discussion

Abscesses of the myocardium are not rare in autopsy material. They are frequently found in cases with pyemia but also occur rarely in myocardial infarcts. In the series of Flaxman[8] almost half of the cases were associated with subacute bacterial endocarditis or with osteomyelitis. One might expect that the marked reduction in the incidence of these two diseases which are barely represented in our current material would be associated with a decrease in the incidence of myocardial abscesses. Paradoxically, we have noted a persistent increase in incidence beginning in 1955. Our current incidence (1.52 per cent) is approximately three times the highest figure (0.56 per cent) reported previously.

The sex incidence of myocardial abscesses has been specified only in the series of Flaxman. Male patients predominated 17 to 12 in his series; female patients predominated 17 to 6 in our series. A reason for the difference in sex incidence in either series is not apparent. Reports of age incidence also vary considerably. Flaxman's patients were younger in general. Most of our patients were older than those previously reported on.

A broad range of conditions united only by the common denominator of pyemia as

Table II. Composite case data—Cont'd

Case number	Year of death	Age, sex	Basic disease process	Surgical procedure	Organism cultured	Antibiotics
16.	1960	59, M	Pyemia after transurethral resection	Transurethral resection	Escherichia coli	Erythromycin Chloromycetin Gantricin
17.	1960	54, F	Carcinoma of ovary with metastases. Intestinal obstruction. Pyemia after administration of nitrogen mustard.	None	Escherichia coli	None
18.	1960	49, F	Gangrene of leg. Phlebitis of leg veins. Pulmonary embolization	None	Staphylococcus aureus	None
19.	1960	68, F	Granulocytic leukemia with disseminated mycotic abscesses	None	Staphylococcus aureus Candida Aspergillus	Erythromycin Cathomycin Gantricin Neomycin
20.	1960	36, F	Subacute hepatic necrosis. Pyemia	None	Staphylococcus aureus	Terramycin Erythromycin Neomycin
21.	1961	73, F	Acute lymphocytic leukemia with disseminated mycotic abscesses	None	Candida	Penicillin Dicrysticillin Terramycin
22.	1961	[illegible], F	Fulminant ulcerative colitis. Pyemia after colectomy	Total colectomy	Escherichia coli	Terramycin Gantricin
23.	1961	43, M	Acute bacterial endocarditis after commissurotomy for rheumatic mitral disease	Mitral commissurotomy	Escherichia coli Staphylococcus aureus	Penicillin Bicillin Streptomycin Terramycin Chloromycetin Gantricin

Table III Electrocardiographic abnormalities

Abnormality	*Total number of cases*	*Present in early ECG*	*Present in late ECG*	*Present in both early and late ECG*
Tachycardia	12	9	6	3
Sinus tachycardia	11	9	6	3
Atrial fibrillation	1	0	1	0
Trigeminy	1	1	0	0
First-degree heart block	2	0	2	0
Increased P-wave voltage	1	1	0	0
Left axis deviation	4	4	3	2
Intraventricular conduction disturbance	3	1	1	1
Right bundle branch block	1	1	1	1
Left ventricular parietal block	1	1	1	1
Nonspecific intraventricular conduction defect	2	2	0	0
Prolongation of T wave	1	0	1	0
Prolongation of Q-T	13	10	6	3
Abnormal QRS-T spatial angle	13	8	8	3
Left ventricular hypertrophy	2	1	2	1

responsible for the production of myocardial abscesses in our 23 patients. Saphir[1,4] previously commented that in almost every instance of pyemia abscesses may be expected in the myocardium. As expected 21 of our 23 patients also had abscesses in other organs most commonly in the kidneys, lungs, and brain. The most common pathogenetic mechanism which we have observed is the lodgement of septic emboli or bacterial clumps into otherwise histologically normal heart muscle. We have not identified histologically demonstrable abnormalities of cardiac muscle which could account for the localization of abscesses.

In 2 of our patients abscesses were limited to the myocardium. Weiss and Wilkins[4] long ago pointed out that myocardial abscesses may develop as solitary local manifestations.

Myocardial abscesses are usually minute and widely disseminated. Patients with sepsis and disseminated abscesses rarely survive long enough to develop large heart abscesses.

Perforation of the heart may rarely occur because of a large abscess. This occurred once in our series. In 1937 Weiss and Wilkins reported 2 instances of rupture of a solitary heart abscess among a series of 31 cases (6.5 per cent) and tabulated 7 additional cases of rupture reported in the literature. Tennant and Parks,[11] in 1959 estimated that 10 per cent of reported heart abscesses had ruptured and suggested that rupture would be more likely to develop in association with abscesses superimposed upon acute myocardial infarcts. An incidence figure as high as 10 per cent for rupture of the heart with a cardiac abscess suggests to us selective reporting of cases. Abscesses accounted for 3 of 611 cases of spontaneous cardiac rupture reported by Krumbhaar and Crowell[12] and for 2 of 98 ruptured hearts analyzed by Davenport.[13]

Very rarely may true abscesses develop in acute myocardial infarcts.[7,9,10] It is likely that necrotic myocardial infarcts reported in the older literature were occasionally misconstrued as abscesses. Tennant and Parks[1] cited 4 cases of abscess formation within acute infarcts and reported a unique fifth case with *Clostridium welchii* empyema of the gall bladder from which Clostridia spread via the blood stream to localize exclusively within a recent infarct which ruptured.

Rupture of a papillary muscle due to a myocardial abscess must be rare. Hackel and Kaufman[9] reported only 2 such cases among 11,550 autopsies performed at The Cleveland City Hospital.

Evaluation of the electrocardiographic abnormalities present in these cases of

myocardial abscess is difficult to make. Two groups of problems must be resolved. The first group concerns the extrinsic factors which can cause electrocardiographic changes. These include hyperpyrexia, electrolyte abnormalities, cachexia, and respiratory and central nervous system disturbances which may produce hypoxia. The second group involves differentiation between progression of primary cardiac abnormalities exaggerated or accelerated by an overwhelming disease state and those phenomena specifically due to myocardial abscesses. Each of these considerations are pertinent to this series.

Several abnormalities are conspicuous by their absence. None of our patients showed electrocardiographic evidence of injury current, nor did any of the patients develop findings which could be interpreted as being indicative of myocardial necrosis. Disturbances in conduction, abnormalities of rhythm, and evidences of ectopic irritable foci were not prominent. The electrocardiographic abnormalities which were prominent were related to nonspecific or ischemic changes consistent with the minute size and diffuse distribution of the myocardial lesions observed at autopsy.

We originally suspected that changes in drug therapy since 1955 might be responsible for the rise in incidence. We had previously demonstrated that a rise in secondary mycotic infections observed at autopsy in leukemic patients could be correlated with steroid, antibiotic, and antimetabolite therapy.[11] Nevertheless, the data from this study do not support a causal correlation between drug therapy and the increase in incidence. Apparently steroids and antimetabolites can be excluded since few patients received these drugs. Bacteriostatic or bactericidal drugs were not usually administered until after an infection developed. Thus they cannot be held responsible for setting the stage for infection. Therapy failed to check the course of these infections. It is possible that patients in the pre-antibiotic era might have succumbed to infections before they had an opportunity to develop multiple abscesses.

An unexpected finding is the fact that in 10 of the 23 patients a surgical procedure was apparently responsible for inducing or disseminating the pyemic process.

Previous studies have demonstrated an overwhelming predominance of staphylococcal infections. The high incidence of *Escherichia coli* infections in this series is another unexpected finding which can be correlated with the number of infections related to abdominal catastrophes and/or abdominal surgical procedures performed in this series.

Clinically, none of these patients had localizing symptoms or signs which drew particular attention to the heart. In each case the existence of myocardial abscesses was obscured by the phenomena of overwhelming sepsis. Almost all patients manifested a record of septic temperatures, tachycardia, and terminal shock-like states.

Summary

Twenty-three cases of myocardial abscess are reported in this autopsy series. The incidence of myocardial abscesses has increased to 1.5 per cent of all of our autopsies during the past 7 years, the highest incidence percentage reported to date.

Abscesses in the heart are usually associated with abscesses in other organs. Almost always there is evidence of generalized pyemia. The association with subacute bacterial endocarditis and osteomyelitis has greatly declined. None of the abscesses in this series was the result of infection of a myocardial infarct. Rupture of the heart due to abscess occurred once.

Staphylococcus aureus and *Escherichia coli* are the most common etiological agents involved in this series. Frequently more than one organism was cultured.

Modern drug therapy is apparently not responsible for the increase in incidence.

Surgical procedures performed during the last month of life were responsible for inducing or disseminating the pyemic process in almost half of the patients in this series.

The electrocardiogram reveals only nonspecific or ischemic changes which fail to provide specific evidence for diagnosis either prospectively or retrospectively.

Myocardial abscesses are usually clinically silent and their presence is usually obscured by manifestations of an overwhelming pyemic process.

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Interpolation of atrial premature beats of infra-atrial origin due to concealed A S conduction

Report of a case of A V nodal parasystole and of a case of premature impulses emerging from a pre-excitation bypass

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Because of the lack of a separate sinus chamber in the mammalian heart, atrial premature beats which occur in a dominant sinus rhythm have an attribute in common with ventricular premature beats which disturb the automatic beating of ventricles in complete A V dissociation In both conditions the dominant pacemaker and the ectopic impulse are located in the same chamber This proximity tends to preclude the interpolation of a premature beat between beats which are generated by two successive regular discharges of the dominant pacemaker no chamber boundary prevents the ectopic impulse from interfering with the dominant center or with its impulse, and from shifting or interrupting the sequence of dominant beats. As a consequence the returning cycle—i.e. the interval between the premature beat and the subsequent dominant one—is expected to be close to or longer than the dominant cycle However exceptions to this rule occur on both levels under consideration Substantially shortened returning cycles and in particular interpolated premature beats encountered under conditions obviously unfavorable to such an event must be due to some peculiar mechanism of pathologic impulse conduction

As far as premature beats in complete A V dissociation are concerned the mechanisms responsible for the occasional shortening of the returning cycle have been analyzed It has been shown that this finding is not so rare as was thought By contrast, only a few authenticated cases of a short returning cycle subsequent to an atrial premature beat in sinus rhythm have been published. Truly interpolated beats are extremely rare at this level in many cases the diagnosis is made erroneously when two atrial premature beats occur in succession and the first beat of the doublet simulates an interpolated one. The few acceptable observations remained as unexplained curiosities until the case recently published by Langendorf Lesser Plotkin and Levin provided the first opportunity to define one of the mechanisms which can protect the sinus pacemaker from the discharge by an early atrial ectopic impulse. The mechanism in question was identified as the concealed conduction[7] of atrial impulses in the direction of the sinus node. Hereafter this case will be repeatedly referred to as "the Miami

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Beach case. It is the purpose of the present paper to describe and analyze two additional cases amenable to a similar interpretation. In some details they differ from the Miami Beach case.

Case 1. Mr. K. Ch., 54 years old, a new immigrant from Rumania, at present employed as a factory worker, was sent for ECG examination because of an irregularity of the pulse. Some months ago, after particularly hard work, he suffered for the first time from palpitations, oppression, and some pain in the chest. On examination he appeared to be a healthy but tense man, with a blood pressure of 165/105 mm. Hg; in the chest x-ray film the heart shadow was enlarged to the left, and the aortic knob appeared to be accentuated. The rest of the findings were normal. His condition was diagnosed as essential hypertension and arteriosclerotic heart disease. As far as could be ascertained, he took no drugs.

ECG tracings were taken repeatedly between Feb. 15 and Aug. 3, 1962 (Figs. 1, 2, and 3).

At all examinations a dominant sinus rhythm was found to be disturbed by a parasystole of "upper" A-V nodal origin; this was proved by P' waves of retrograde contour which preceded the ventricular complex with a shortened P-Q interval, by the variable coupling of the P' waves to the preceding sinus P wave, by the characteristic spacing of the ectopic beats, and by the occasional appearance of atrial fusion beats. On different days both the sinus rate and the rate of the ectopic center varied; during a continuous examination sudden slowing of the ectopic center was observed from time to time for a few beats. (Fig. 2, *lower strip*.)

The interest centers on the findings of February 15. On this particular date the sinus rate was slow; the sinus cycle, as measured directly when two sinus P waves appeared in immediate succession, varied between 1.18 and 1.28 sec. 100. The premature P' waves followed the preceding sinus P wave at variable distances. When the coupling was relatively long—roughly when the ectopic P' occurred after the termination of the preceding T wave—the postectopic P'P interval (the "returning cycle") was of the expected magnitude, i.e., somewhat longer than one sinus cycle. The time required for the impulse to ascend from the atria to the sinus center and the depression of this center by the extraneous impulse[8] accounted for the additional interval length. The normograde conduction of the ectopic impulse to the ventricles was undisturbed.

However, when the ectopic P' wave coincided with the descending limb of the preceding T wave, the sequence of events was different. (1) The conduction of the impulse to the ventricles was either completely blocked (Fig. 1, *strip 2*) or delayed with aberration of the intraventricular conduction. (2) Likewise, the retrograde conduction to the atria was delayed to a variable degree; this delay was proved by the observation that the short-coupled P' terminated a prolonged P'P' interval and initiated a shortened one, and that the sum of both intervals was close to two parasystolic cycles. Such variations in the manifest cycle of parasystolic beats—due to delayed conduction of impulses from the ectopic center to the contracting myocardium—are not unusual. (3) The salient trait of the short-coupled P' waves was their returning cycle; it was shorter than one sinus cycle.

For the sake of succinct exposition, the atrial deflections will be numbered as follows: P_1 stands for the atrial wave which immediately precedes the ectopic one; P'_2 stands for the ectopic wave itself, the prime sign denoting the ectopic origin; P_3 stands for the sinus wave subsequent to the premature beat. The following P waves will be similarly numbered and marked according to their order of appearance and their origin.

As can be seen at a glance and confirmed by measurement, the following relationships exist when the length of $P_1P'_2$ is 0.52 sec. or less. (1) The interval P'_2P_3 is substantially shorter than one sinus cycle (whose order of magnitude is 1.2 sec.); the values of the reproduced P'_2P_3 intervals are 0.95, 0.91, 0.96, 0.82, and 1.0 sec. It follows that the impulse associated with P'_2 has failed to discharge the sinus pacemaker in these instances. (2) The sum $P_1P'_2 + P'_2P_3$ (i.e., the interval P_1P_3) is somewhat longer than one sinus cycle; the increment varies between

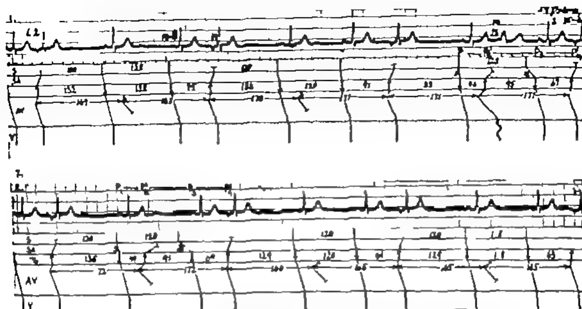


Fig. *1* Case 1. T sections of Lead II recorded on Feb. 15, 1962. Sinus rhythm interrupted by upper A-V nodal parasystole. Conventions of the diagrams in this and in the following figures: *Level S*, Assumed discharges of the sinus pacemaker. *Level SA*, Assumed S-A and A-S conduction; the absolute values of conduction times are arbitrary. *Level A*, Observed atrial deflections. Downward arrows denote P waves of sinus origin, upward arrows P′ waves of ectopic origin. *Level AV*, Atrioventricular conduction. The position of the ectopic A-V parasystolic center is conjectural. *Level V*, Observed ventricular deflections; the bizarre ones are marked by a wavy line. Premature trial beats (P′) which occur early after the preceding sinus P wave (P) are associated with retrograde A-S impulse that does not reach the sinus pacemaker but causes delay in the subsequent sinus impulse conduction. The conduction from the ectopic center to the tria and to the ventricles depends on the timing of the discharge with respect to the preceding sinus beat. P′ is interpolated between P and P_1.

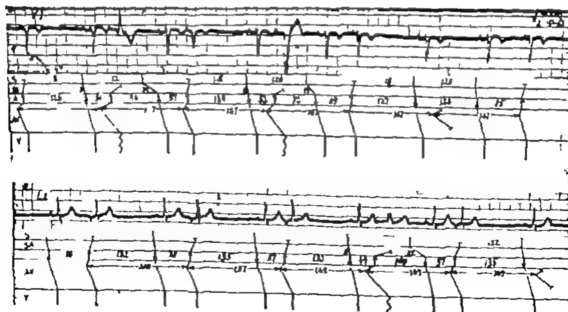


Fig. *2* Case 1. Additional instances of interpolated ectopic trial beats with delay of subsequent S-A conduction. *Upper strip*, Lead V. *Lower strip*, Lead II. The lower strip illustrates sudden transient slowing of the parasystolic rhythm.

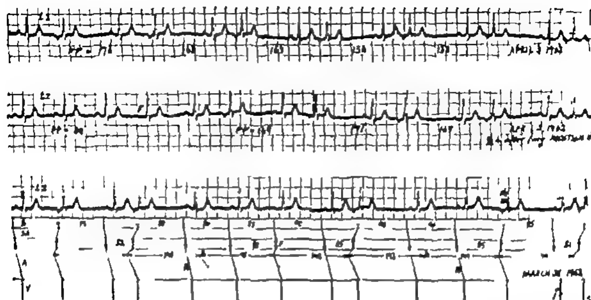


Fig. 3. Case 1. Records taken on April 3 and March 31, 1962. Lead II. The sinus rate is faster than at the first examination. There is no opportunity for the interpolation of atrial premature beats because none of them occurs early enough after the preceding sinus P wave. Allorhythmia consisting of fairly regular long bigeminal sequences is due to the circumstance of the sinus pacemaker being discharged by the ectopic retrograde impulses while the ectopic center is protected from the sinus impulses. Deviations from this orderly disorder (*lower strip beginning of the middle strip*) are caused by variations in factors which are discussed in the text. Atrial deflections marked *F* are fusion P waves.

0.17 and 0.24 sec. On the most probable premise that the sinus impulse which gives rise to P is emitted at the right time, the conclusion follows that its conduction to the atria is delayed by this increment. The premise would be verified if it could be shown that P-P is shortened by the same amount. Unfortunately, in this as well in the Miami Beach case a sinus P_3 never makes its appearance because it is always anticipated by an ectopic P'_3; this is the result of the parasystolic nature of the ectopic beats.

In the search for an explanation of the P conduction delay, the analogy with a similar delay that affects the A-V conduction comes to mind. Subsequent to a ventricular premature beat which is interpolated between beats of sinus origin, the P-R interval is usually prolonged.[6,7,8] The P-R prolongation is convincingly explained by a retrograde impulse which is emitted by the ventricular ectopic focus and penetrates into the A-V junction; this penetration creates a refractory state of the conducting tissues and causes the slowing of the subsequent sinus impulse if the timing of the two impulses is appropriate. The conditions easily lend themselves to analysis when the conduction can be measured directly from start to finish, as in the case of the A-V junction. In the case of the S-A conduction the start is a matter of conjecture. Nevertheless, the sequence of events can be reconstructed with the help of the A-V analogy. The interpretation—identical with that given by Langendorf and his associates in their case—is graphically illustrated in the diagrams of Figs. 1 and 2. It is based on the assumption that the ectopic impulse, after having generated the atrial contraction P_2, progresses toward the sinus node but does not reach the pacemaker. The existence of this concealed A-S conduction is revealed by the subsequent delay of the next S-A impulse which generates the wave P_3.

On later dates numerous long records were taken, samples of which are reproduced in Fig. 3. The sinus rate was faster than on the first occasion. Never again was the ectopic P' wave inscribed early enough to be superimposed on the preced

ing T wave and no opportunity for interpolation presented itself. Instead there were long monotonous bigeminal sequences: impulses of the nodal parasystolic focus discharged the sinus pacemaker which had to start its cycle from the beginning. The P'P' interval was determined by the parasystolic rate; the P'P interval by such factors as the duration of the A-S conduction, the intrinsic length of the sinus cycle, the degree of the depression exerted by the ectopic impulse on the sinus pacemaker, and the velocity of S-A conduction. If all these factors were constant, the result would be a perpetual unvarying allorhythmia in which the ectopic and sinus rhythm join to form a pattern of interference.[11] The actually observed deviations from such an orderly sequence such as changes in the coupling of the premature beats, the nonappearance of *some of them*, and the occurrence of fusion P waves were caused by the variations in the determining factors.

Case 2. Mr. S.S., 64 years old, born in the Caucasus, a resident of this country since 1925, performs physical work in a stone quarry. The only complaint was in regard to palpitations. Allegedly no drugs were taken. The general examination was negative except for the arrhythmia; the blood pressure was 140/80 mm. Hg. The chest x-ray film showed signs of emphysema, dilatation of the heart to the left, and bulging aortic knob with calcification. The records reproduced in Figs. 4, 5, and 6 were taken during a single visit of the patient on June 3, 1962. Numerous long records were also taken during a week of ward observation in August, 1962, but are not reproduced.

CONVENTIONAL LEADS (Fig. 4). The basic rhythm is of sinus origin and presents the features of the pre-excitation syndrome (WPW) proved by the P-Q interval of 0.1 sec. and by a delta wave which broadens the QRS complex to 0.12 sec. The rhythm is disturbed by frequent premature beats with a somewhat variable coupling; they give rise to long bigeminal sequences. The premature beats lack a clearly defined P wave and could be easily diagnosed as ventricular premature beats because of their bizarre shape. In the third strip (representing a section of Lead II) there are two bizarre beats in succession, but the second one is preceded by a P wave which is marked P_3.

ESOPHAGEAL LEADS RECORDED SIMULTANEOUSLY WITH LEAD II (Figs. 5 and 6). Rather surprisingly, it turns out that the ventricular component of the premature complex is preceded by an atrial deflection which is practically undetectable in the limb leads and questionable in the chest leads. The premature P' waves differ from the sinus P waves on both esophageal levels examined. In Lead E40 the premature atrial complexes are equiphasic with a pronounced terminal negative component which is lacking in the sinus P waves. In Lead E35 (not reproduced) the premature P' is monophasic, positive, and higher than the sinus P wave of this lead.

Any doubts about the atrial nature of the equiphasic deflections seen in Lead E40 can be dispelled by two observations. (1) This deflection is not a part of the bizarre premature ventricular complex because it is conspicuously absent in those bizarre ventricular complexes which are preceded by a sinus P wave (e.g., the complex subsequent to P in Fig. 6). (2) No other evidence *of atrial* activity of any origin is seen in the esophageal leads near or after the premature beat.

It is obvious that the atrial and the ventricular deflections are much closer to each *other in* the premature beats than in those of sinus origin. The P-Q interval of the premature beats is constant and measures approximately 0.04 sec.; thus, a direct conduction from the atria to the ventricles is ruled out. The constancy of the P-Q interval indicates a common focus from which both atrial and ventricular contractions are generated, and this focus must be located between the atria and the ventricles. *However*, it is most improbable that the A-V node is the origin of the impulse whose ascending limb generates an atrial wave quite different from the familiar upwardly directed retrograde wave of A-V nodal origin. The vector of the atrial premature wave is directed at a right angle to the frontal plane, as evidenced by the isoelectric P waves of all limb leads. This unusual direction of the impulse spread proves an unusual point of entry to the atria.



Fig. 4. Case 2. Conventional leads. The basic rhythm is of sinus origin and present the features of the pre-excitation syndrome. This rhythm is disturbed by frequent premature beats which give rise to long bigeminal sequences. The premature complexes are bizarrely shaped and lack a clearly defined P wave. Without further investigation they could be diagnosed as ventricular premature beats. In the third strip from the top two bizarre complexes appear in succession but the second one is preceded by P wave marked P_3. Interpretation in text.

Additional information about the location of the focus of the premature beats is provided by the shape of their ventricular deflections. For all their bizarreness these deflections deviate from those of the dominant beats only in the final element of the QRS complex and in the ST-T segment.[12] When the premature and the dominant QRS complexes of any lead are superimposed on one another their initial portions which consist of the delta wave are almost identical for about 0.08 sec. It appears that the dominant and the premature impulse begin their spread through the ventricular myocardium in an identical manner and that the descending limb of the premature impulse uses the same terminal at which the dominant impulse enters the ventricular myocardium.[8] Only at a later stage of the impulse spread do modifying influences come into play.

The bypass theory of pre-excitation offers a satisfactory explanation of all observed phenomena if it is assumed that the ectopic focus is located in or near the bypass pathway used by the impulses of the dominant beats. Such a location of an ectopic focus has been described in strong support of the theory[12] and in refutation of previously held views.[4] In the present case the bizarre ventricular complexes are due—according to the assumption—to the unmodified spread of the ectopic impulse emerging from the bypass, while most of the dominant impulses split and enter the ventricles from two separate points: first, from the bypass terminal and somewhat later also from the normal inferior A-V terminal. The final shape of the ventricular complex results from the interference between the two impulse spreads.[13,14]

This interpretation helps us to understand the anomaly of those sinus impulses which appear exceptionally early after an ectopic one. These sinus impulses are transmitted from the atria to the ventricles through the usual bypass, since the P-Q interval of 0.1 sec. does not differ from that of the regular sinus beats. However, the exceptional sinus impulses produce ventricular complexes of the bizarre type which are indistinguishable from the complexes of ectopic origin. It must be concluded that the normal A-V conduction path is not available for the transmission of impulses during a certain span of time after the passage of the ectopic impulse. Since the retrograde ectopic impulse is assumed to reach the atria through the

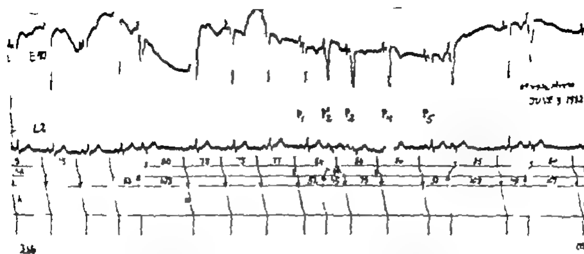


Fig. 5. Case 2. An esophageal lead at electrode level 40 cm. from the nares was taken simultaneously with Lead II. The esophageal lead reveals that the ventricular deflections of the premature beats are preceded at a very short constant distance by biphasic atrial deflections which differ in shape from those of sinus origin. That this initial deflection is no part of the ventricular complex is proved by the complex which follows the atrial wave marked P although of the bizarre variety the complex lacks the initial biphasic deflection. The proximity of the atrial and ventricular deflections places the ectopic center in the A-V space. Three of the illustrated atrial premature beats are followed by long returning cycles. The exception (P') is interpreted as an interpolated beat due to a mechanism similar to that in Case 1. In this case, however, the delayed atrial wave P is again followed by an atrial wave P of sinus origin because of the sporadic nature of the premature beats. The shortening of P P supports the interpretation.

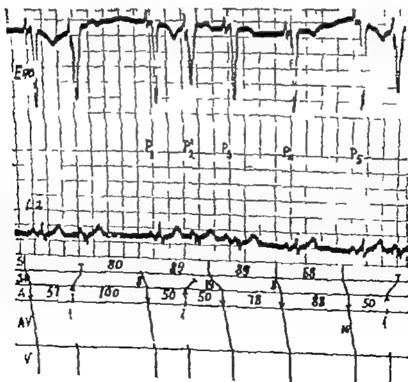


Fig. 6. Case 2. Another instance of an interpolated atrial premature beat.

bypass and not through the normal conduction pathway the latter must have been enterred by the ectopic impulse from the atrial end this secondary downward sweep of the ectopic impulse does not produce any ECG manifestation because of the refractoriness of the ventricles. As in other instances of concealed conduction it has to be deduced from a subsequent anomaly the deviation of the closely following sinus impulse to the bypass the only pathway which has in the meantime recovered its conductivity

THE RETURNING CYCLE OF THE PREMATURE BEATS As in Case 1 the interval between the atrial premature deflection and the next sinus P wave in most instances follows the usual rule and is longer than the nearby sinus cycle The problem of the case concerns five observed exceptions to the rule three of which are reproduced Figs. 4 5 and 6 each contains one instance of an atrial premature deflection which is followed by an atrial interval that is shorter than any ordinary sinus cycle in the adjacent portion of the record It is important to realize that the P wave which follows such an exceptional premature beat presents the characteristic features of a sinus P wave both in Lead II and in the esophageal leads and cannot be confused with a repeated atrial premature beat—although its companion QRS complex is of the bizarre variety as previously discussed

In the interpretation of the short returning cycles the uneven sinus rhythm must be taken into account in this case. In different portions of the record taken on June 3 1962 the sinus cycle varies between 0 72 and 1 04 sec but the changes are gradual and the difference between adjoining sinus cycles does not exceed 0 1 sec. whenever it can be measured Therefore returning cycles of 0 45 and 0.5 sec length cannot be explained by a sudden shortening of the sinus cycle.

The most probable explanation is suggested by the structure of the sequences which precede and follow the exceptional premature beats. These sequences resemble those of Case 1 and can be interpreted in the same way although in this case the variability of the sinus rhythm obviates exact computations. On the other hand the case offers an advantage which is missing in Case 1 and also in the Miami Beach case. If again P_1 denotes the sinus P wave which precedes the exceptional ectopic beat, P_2 denotes the atrial deflection of ectopic origin etc. in the present case beat P_3' is followed by a sinus beat P_4 and not by an ectopic P_4' as in the other cases. This sequence is due to the sporadic nature of the premature beats which contrasts with the regular parasystole of the previous cases. If it is assumed—as in Case 1—that the impulse associated with P_3' proceeds in the direction of the sinus node without reaching the pacemaker but creating a refractory state in its surroundings and thus causing a delay of the P wave it is to be expected that the interval P_1P_3 should be longer and the interval P P_4 shorter than one ordinary sinus cycle as represented by the immediately following interval P_4P_5 (provided that the transmission delay is limited to one beat.)

Table I presents the pertinent data. In all five instances the interval P_1P_3 is considerably longer than the interval P_3P_4, whereas the length of P P is intermediate. These are the expected relationships. In order to obtain some rough estimate of the delay in transmission two assumptions are made (1) that the sinus rhythm remains constant for the two cycles which give rise to P_1P and P_3P_4 and (2) that only P is delayed Thence the sinus cycle at the time of the ectopic beat is estimated as the mean of P_1P_3 and P_3P and the delay of P_3 is deduced by the subtraction of this value from P_1P_3. The comparison of the estimated sinus cycle with the adjacent observed one reveals excellent agreement in two instances in the rest the differences fit into the variability pattern of the tracing as defined earlier On the strength of these results the interpretation appears to be vindicated

The number of interpolated premature beats found in this case is too small to allow an examination of the conditions under which the phenomenon is to be expected In particular its dependence on the length of the coupling or on that of the preceding sinus cycle cannot be established

Long tracings of conventional and esophageal leads taken daily during a week

Table I. Estimate of the sinus cycle at the time of interpolation and estimate of the S-A conduction delay of the subsequent sinus impulse (Case 2)*

	A. Prolonged P-P interval of sinus origin	B. Shortened P-P interval of sinus origin	C. Estimated sinus cycle at time of interpolation	D. Observed adjacent sinus cycle	E. Estimated delay of post-ectopic impulse conduction	
	P_1P	P_2P	$\frac{1}{2}(P_1P + P_2P)$	P_3P	A-C	
1	95	77	86	94	9	Not reproduced
2	109	89	99	104	10	Fig. 4
3	100	78	89	88	11	Fig. 6
4	97	75	86	86	11	Fig. 5
5	118	50	84	74	34	Not reproduced

*Numbers are in hundredths of a second.

of the patient's stay in the hospital 2 months after the first examination failed to reveal a single instance of interpolation. The records consist of monotonous bigeminal sequences due to premature beats of the described type, rarely interspersed with short runs of regular sinus rhythm. All returning cycles are longer than the sinus cycles.

Discussion

The interpolation of atrial premature beats which is due to concealed conduction from the atria to the sinus node is dealt with in the paper of Langendorf and associates. Here it is only necessary to discuss the peculiarities of the present cases and especially the features by which they differ from the Miami Beach case.

1. The origin of the ectopic beats is infra-atrial in both present cases. It is well known that nodal premature beats can be interpolated under appropriate conditions of timing. However, in most cases of this kind the retrograde impulse—if it is at all emitted—is stopped within the junctional tissues and does not activate the atria. By contrast, whenever the impulse succeeds in spreading through the atrial myocardium, its further progress toward the sinus node must be subject to the same rules which govern impulses that originate in the atria themselves. This similarity can be demonstrated when atrial contractions of different origin appear side by side. In a recently observed case of a dominant sinus rhythm an atrial premature P wave and a retrograde P' wave (generated by a ventricular premature beat) occurred in the same short strip and were followed by long returning cycles of identical length (unpublished observation). From this point of view, only the evidence of atrial activation is relevant whatever the origin of the ectopic impulse in the atria or below the atrial level may be. As a matter of fact, the pattern of these arrhythmias is so uniform that in several published cases the A-V nodal origin has been overlooked and the erroneous diagnosis of atrial parasystole has been made, while, in reality, A-V nodal parasystole was present.

It follows that the same significance must be attached to the anomalous behavior of the returning cycle subsequent to a premature atrial contraction of infra-atrial origin as to the phenomenon associated with a true atrial premature beat.

2. In Case 2 the chief evidence of the atrial activation was obtained by the use of esophageal leads. On the strength of the conventional leads the premature contractions probably would be mistaken for ventricular premature beats. The true nature was revealed by the detection of atrial deflections and of their proximity to the ventricular complexes in Leads E40 and E35. Since the recording of esophageal leads is still infrequently used in routine work, it is possible that some pertinent cases remain unrecognized on this

account. The shape of the QRS complex does not always differentiate between ventricular and supraventricular premature beats. The importance of recording esophageal leads when atrial deflections are absent or poorly delineated in conventional leads must be re-emphasized.[8, 9]

By paying attention to the direction in which the vector of the P' wave points and to the shape of the initial QRS portion in the premature beats, one arrives at the conclusion that the ectopic focus of Case 2 is located at an atypical site—within or near the bypass of the pre-excitation mechanism.

Another explanation for the rarity of the studied phenomena is provided by the capriciousness of their manifestation. In each case they could be detected only during one among numerous examinations which involved very long records. Obviously, concealed A-S conduction depends on a narrow range of critical conditions and differs in this respect from the analogous phenomenon in the A-V junction, where concealed conduction can be identified as the mechanism operative in a variety of arrhythmias.[19-21]

3. Case 2 is the only one in which the premature beats are of a nonparasystolic nature. Because of their sporadic appearance the interpolated beats are followed by a series of sinus beats which show for the first time that the prolonged atrial interval of sinus origin which contains the sandwiched-in premature beat is followed by a correspondingly shortened interval. Although the relationships are somewhat blurred by the sinus arrhythmia, the observation supports the conclusion that the first postectopic sinus impulse travels with some delay, whereas the next one restores the regular sequence of atrial beats.

4. Langendorf and his associates classified their case as one of "pseudo-interpolation" because they could show that the sinus impulse which followed the delayed one was blocked and not interfered with. The delayed sinus beat (P in the notation of the present paper) would be followed by a postponed compensatory pause[22] but for the intrusion of the next parasystolic ectopic beat. By contrast, both present cases represent instances of "true interpolation." The free passage of the retrograde P_4' impulse indicates that at the time when the sinus P_4 impulse was due no conditions of block would exist between the sinus node and the atria. In Case 2 the manifest conduction of the impulse that gives rise to P_4 directly proves the point.

In spite of differences in detail, the Miami Beach case and the two cases presented in this paper are very similar. Even quantitatively, the delay in the S-A conduction is of the same order in all three cases. So the mechanism which underlies this delay cannot be considered to be a mere freak, and the conclusion is strengthened by the comparison with the standard phenomenon of the A-V conduction delay caused by interpolated ventricular premature beats. Until recently the sinoatrial portion of the conduction system was the only one which did not yield any evidence of concealed impulse conduction. Now the gap is filled and this fundamental aspect of propagation of the cardiac impulse[7] is shown to be common to all parts of the myocardial conducting tissues.

Summary

In each of two cases presented, atrial premature contractions which are caused by infra-atrial retrograde impulses disturb a dominant sinus rhythm. In one of the cases these impulses are generated in an A-V nodal parasystolic center, whereas in the other case—presenting the features of the WPW syndrome—the location of the ectopic impulse center is atypical. Subsequent to the atrial contraction most of the retrograde impulses follow the usual rule: they ascend to the sinus pacemaker, discharge it, and start a new sinus cycle. As a consequence, the returning cycle—i.e., the interval between the ectopic P wave and the next sinus P wave—is in most instances somewhat longer than one sinus cycle. The present study is concerned with some exceptions to this rule, i.e., with the returning cycles which are shorter than one sinus cycle. The analysis of such exceptions indicates that they occur when the retrograde impulse does not reach the sinus pacemaker but penetrates into the tissue through which the S-A impulses are transmitted. This concealed A-S conduction causes some delay in the transmission

of the subsequent sinus impulse to the atria. As a result the ectopic P wave is sandwiched in between two sinus P waves separated by an interval that exceeds an ordinary sinus cycle.

These cases represent the second and third published instances of concealed impulse conduction affecting the S-A section of the conduction system and the first ones in which this interpretation is applied to true interpolation of atrial premature beats (as contrasted with pseudo-interpolation). Case 2 provides the first opportunity to check the interpretation by showing that the P-P interval which follows the prolonged one is correspondingly shortened.

The premature atrial contractions of Case 2 would probably be overlooked without the study of esophageal leads, whose usefulness is stressed. The analysis of the sequence and shape of the ectopic atrial and ventricular complexes which occur in this instance of the WPW syndrome leads to the conclusion that the ectopic center is located in or near the bypass that is responsible for the pre-excitation of the ventricles.

The interpolation of atrial premature beats depends on a narrow range of timing and other undefined conditions and therefore, is observed only exceptionally even in the same subject. This is probably the chief explanation for the rarity of the arrhythmia. However, the detection of two additional cases proves that it cannot be considered to be a singular oddity but reveals a hitherto unrecognized localization of the general mechanism which underlies the concealed impulse conduction in the myocardium.

Addendum

After this paper had been accepted for publication there came to our attention an additional instance of interpolated atrial premature beats which were followed by slowed sinoatrial conduction. In this case the origin of the premature impulses could be traced to an atrial parasystolic focus.

It is to be expected that the phenomenon described in this paper—although rare and evanescent—will be found with increasing frequency if carefully looked for.

I should like to thank Dr. Richard Langendorf and Dr. Alfred Pick for examining the records and offering valuable advice.

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Effects of breathing oxygen on atrioventricular conduction

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Pharmacologic concentrations of oxygen are used in the therapy of various cardiopulmonary disorders and in anesthesia, yet the cardiac and circulatory effects of breathing oxygen are not widely appreciated. Such effects have intrinsic physiologic interest and are of clinical interest since they are associated with the use of one of the common therapeutic agents.

It is well established that the breathing of oxygen decreases the heart rate and cardiac index of resting normal man.[1-4] It also decreases the heart rate of normal man under certain other situations. Such changes are the result of decreased sinoatrial nodal activity. The present study is an evaluation of the effect of breathing 100 per cent oxygen on atrioventricular conduction.

Methods

Sixteen patients with atrial fibrillation, 8 patients whose electrocardiograms demonstrated normal P-R intervals and ST-T changes of digitalis effect, 7 patients with prolonged P-R intervals, 2 patients with incomplete A-V block with Wenckebach phenomenon, and 11 normal subjects were selected for study. No patient or subject showed clinical evidence of hypoxemia. All rested 30 minutes in the laboratory or in their hospital beds before being tested. Air or 100 per cent oxygen was breathed from a high-flow, low-resistance mask system in random sequence. Each gas cylinder was assigned a number and the sequence of administration was determined from a random number table. The patient did not know the sequence used. After each gas had been breathed for 10 minutes, an electrocardiogram was recorded for a period of 2 minutes, and the heart rate was counted over the entire period. P-R intervals were determined to the nearest 0.01 second as the mean of at least ten complexes recorded at 50 mm. per second. The P-R interval was considered to be prolonged if it exceeded 0.20 second. The lead showing the most distinct P waves was selected for recording. Lead II was used in instances of atrial fibrillation. Arterial blood oxygen saturation was determined spectrophotometrically in 6 of the patients with atrial fibrillation.

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Statistics

In the group with sinus rhythm the effect of breathing oxygen on heart rate and A-V conduction was evaluated using a paired comparison *t* test with each patient serving as his own control. This permitted evaluation of the statistical significance of small changes associated with the breathing of oxygen in a population with relatively large variability, since the inherent variability of the population was random whereas the changes due to the breathing of oxygen were not. The data from the fibrillating patients were analyzed as follows. The changes in the group for which arterial blood determinations were made were analyzed separately and were compared with those in patients in whom oxygen saturations were not determined; thus the statistical significance of the change due to the breathing of oxygen was determined separately in each of the two groups. The changes associated with the breathing of oxygen in the two groups were then compared. It was thus possible to determine whether the breathing of oxygen was associated with a decrease in ventricular response and whether the amount of change was any different in the two groups, one known not to be hypoxic and the other presumed not to be hypoxic.

Results

In the normal subjects (Table I) and patients having sinus rhythm with and without A-V conduction abnormality, small but statistically significant decreases in heart rate were associated with the breathing of 100 per cent oxygen. In the normal subjects the mean heart rate decreased from 72±8 to 66±8 ($p = 0.001$). The P-R interval (0.17±0.02 second) was not affected. In those patients with normal atrioventricular conduction but S-T-T changes associated with digitalis effect the heart rate decreased from 73±17 to 66±15 ($p = 0.025$). The P-R interval (0.17±0.02 second) was unaffected. In those patients with initially prolonged A-V conduction but with 1:1 atrioventricular conduction the heart rate decreased from 80±8 to 76±7 ($p = 0.005$) and the P-R interval increased from 0.24±0.03 to 0.26±0.05 second ($p = 0.025$). In those with second-degree atrioventricular block with Wenckebach phenomenon the atrial rate decreased in both instances without a change in the ratio of atrial and ventricular rates. The P-R interval of the first conducted sequence of each Wenckebach series increased.

Each of the patients with atrial fibrillation demonstrated some decrease in the ventricular response during the breathing of oxygen. The group in which arterial blood oxygen saturation was determined (mean 94.6±2 per cent) showed a decrease in ventricular rate of 66±9 to 60±10 ($p = 0.005$). The group in which arterial oxygen saturation was not determined demonstrated a decrease in ventricular rate from 91±26 to 85±27 beats per minute ($p = 0.001$). The probability that the changes in heart rate with the breathing of oxygen in the first group are the same as the changes in the second group is greater than 0.5.

Discussion

Von Euler, Liljestrand, and Zotterman[7] using anesthetized cats found no evidence of change in chemoreceptor activity at arterial oxygen saturations above 97 per cent. Witzleb and associates, also recording action potentials from the carotid body nerve in anesthetized cats, found no change in the number of impulses recorded when the arterial pO₂ was above 110 mm. Hg. Consequently, it has been commonly assumed that oxygen or the lack of it exerts little if any influence on the chemoreceptor activity of normal man breathing air at sea level.[8] Yet, since the observations of Parkinson in 1912,[2] subsequently confirmed by numerous others,[-4] it has been known that breathing 100 per cent oxygen decreases the heart rate of resting normal man. In dogs Whitehorn and Bean have demonstrated that this is a vagal effect, and others[4] have shown that this effect is not observed in atropinized man. Consequently, it seems that hyperoxic breathing produces a vagus-dependent decrease in heart rate. Furthermore, it has been shown that this decrease is progressive over the entire range of oxygen concentration from 21 to 100 per cent and is not confined to the range closest to 21 per cent. This phenomenon therefore does not represent

Table I Effects of breathing 100 per cent oxygen on heart rate and A V conduction

Electrocardiogram	*Number of subjects*	*Atrial rate (beats/min.)*		*P R interval (sec.)*	
		Air	*Oxygen*	*Air*	*Oxygen*
Normal	11	72 ± 8*	66 ± 8	0 17 ± 0 02	0 17 ± 0 02
		p = 0 001		p = NS	
ST T changes of *digitalis*, normal A-V conduction	8	73 ± 17	66 ± 15	0 17 ± 0 02	0 17 ± 0 02
		p = 0 025		p = NS	
Prolonged A-V conduction	7	80 ± 8	76 ± 7	0 24 ± 0 03	0 26 ± 0 05
		p = 0 005		p = 0 025	
Incomplete A-V block (Wenckebach)	2	94 ± 16	83 ± 10	0 22 ± 0 02†	0 24 ± 0 02
Atrial fibrillation‡	6	66 ± 9	60 ± 10		
		p = 0 005			
Atrial fibrillation§	10	91 ± 26	85 ± 27		
		p = 0 001			

*Mean ± one standard deviation.
†P-R of first sequence of Wenckebach series.
‡Mean arterial oxygen saturation = 94 8 ± 2 per cent.
§Arterial oxygen saturation not available, no clinical evidence of undersaturation.

merely the relief of occult hypoxemia, but is rather a portion of a continuous spectrum of chemoreceptor activity in which the vagus plays a dominant effector role.

The group of patients with atrial fibrillation demonstrates a decrease in A V conduction during the breathing of oxygen as indicated by the slowed ventricular response. In the group with sinus rhythm although sinoatrial activity decreased A V conduction was not prolonged except in those patients whose conduction was initially delayed. The failure of the breathing of oxygen to prolong A V conduction in normal subjects is in agreement with the observations of Anthony and Kummel.[15] In a sense those patients with atrial fibrillation were similar to those with prolonged P R interval because with but a single exception they demonstrated a relatively slow ventricular response to atrial fibrillation that is, the A V conduction had already been altered by digitalis. This observation would suggest that the mild vagal stimulus of hyperoxic breathing alters A V conduction only if it is abnormal initially. This is consistent with a more general clinical observation that vagal stimulation is usually more apt to be effective if the A V conduction is first altered by digitalis. The presence of digitalis alone is not sufficient to allow hyperoxic breathing to affect A V conduction because in those patients taking digitalis without initially abnormal A V conduction no further prolongation occurred.

The changes in heart rate and A V conduction are small yet they are consistent and seem to be a phenomenon associated with the use of pharmacologic concentrations of oxygen.

Summary

Hyperoxic breathing slows atrioventricular conduction in patients with already prolonged A V conduction time and decreases the ventricular response to atrial fibrillation.

As in normal man hyperoxic breathing slows the heart rate of patients with sinus rhythm who are taking digitalis and or who have varying degrees of atrioventricular block.

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Observations in patients with implanted cardiac pacemaker

I. Clinical experience

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The use of an electric pacemaker by Zoll and his associates[1] for stimulation of the heart in man opened a new era in the treatment of heart block with bradycardia and Adams-Stokes syndrome. Indirect stimulation by way of externally applied electrodes requires strong electrical currents which cause painful contractions of the pectoral muscles and soreness at the site of the electrodes. In 1957 Weirich and associates[2] introduced wire electrodes which were sutured to the myocardium and permitted direct stimulation of the heart by weak currents. The wires leading to an externally placed source of power traversed the chest wall. Piercing of the skin carries a risk of infection. Furman and associates[3] used electrodes which were introduced by way of a catheter through the jugular vein and applied to the endocardial surface of the right ventricle. The advantages of this method are the relative ease of application and avoidance of thoracotomy; the disadvantages are the possibility of infection, thrombosis, breaking of wires, occasional perforation of the wall of the right ventricle, and shifting of the electrode. The method is suitable primarily for short term stimulation of the heart. Glenn and his associates avoided piercing of the skin by using an externally located radio-wave transmitter and a receiver buried under the skin from which wire electrodes led to the myocardium. Construction of transistorized miniature pacemakers with long lived batteries[5] allowed the implantation of the power unit subcutaneously, with wires leading through a subcutaneous tunnel to the myocardium. The output of the pacemaker is large enough to provide sufficiently strong stimuli even when formation of scar tissue during the first few weeks after implantation has increased tissue resistance and threshold requirements for stimulation.

Method and material

During the past 21 months, the Kantrowitz modification of an implantable miniature pacemaker has been used in the Maimonides Hospital. It delivers stimuli of 2 msec. duration at a rate of about 60 per minute. When desirable, the rate of formation of stimuli can be increased up to 120 per minute by application of an external control unit at the site of the buried pacemaker.

Twenty-seven patients were treated with

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the implantable pacemaker Their ages ranged from 39 to 85 years the majority (18) were in the seventh or eighth decade of life There were 12 men and 15 women. In 25 patients coronary arteriosclerosis was diagnosed as the underlying pathology and in 2 patients it was myocarditis of rheumatic and unknown origin respectively

A history of syncopal attacks was obtained from 25 patients the seizures covered periods from several weeks to 5 years. However in one patient who had suffered an Adams-Stokes seizure for only a few hours a pacemaker was inserted without delay because electrocardiographic records proved the attacks to be caused by ventricular flutter fibrillation One patient suffered fainting spells due to ventricular flutter fibrillation in the absence of heart block. Since sinus bradycardia was present a pacemaker was implanted in the hope that the occurrence of seizures would be prevented by maintenance of a higher heart rate In another patient with heart block and fixed bradycardia, chronic congestive heart failure provided the main indication for use of an artificial pacemaker

The nature of the Adams-Stokes attacks was revealed in 19 patients by electrocardiograms observed during seizures or in the pre-fibrillatory state. In 7 ventricular standstill was the cause In 12 patients, ventricular flutter fibrillation was demonstrated either alone (6) or alternating with ventricular standstill (6)

Preceding implantation of a permanent pacemaker stimulation by way of catheter electrodes was used in 23 patients as a temporary measure in order to provide quick relief and to prevent the development of ventricular standstill or fibrillation in the course of anesthesia and surgery

Results

1 Fatalities Early postoperative deaths occurred in 6 patients. In no case was failure of the pacemaker directly responsible for a fatal outcome In a single case failure of electrical stimulation was followed by satisfactory control of the heart by the patient s own idioventricular rhythm When an attempt was made to exchange the pacemaker without assuring proper stimulation of the heart by use of catheter electrodes, cardiac standstill and ventricular fibrillation developed The patient succumbed later to irreparable damage to the nervous system caused by protracted interruption of the circulation Another patient died of recent myocardial infarction which was proved by postmortem examination. One patient developed severe chest pain 6 days after operation and died suddenly during the attack. Bacterial endocarditis subsequent to insertion of a catheter electrode led to a fatal outcome in the fourth patient In the other 2 patients congestive heart failure and intestinal bleeding were the causes of death

2 Complications Disturbance of artificial stimulation occurred frequently during temporary use of catheter electrodes which may easily slip away from the endocardial surface. This is readily remedied by increasing the voltage or by adjusting the position of the catheter electrode. In 6 patients disturbances in the flow of stimuli from the implanted pacemaker to the heart occurred these were usually due either to the breaking of a wire close to the pacemaker or near the heart or to the slipping of the myocardial electrode. Sometimes such disturbances occurred repeatedly in a patient especially when an attempt was made to weld broken wires, which was followed by a new break at the site of welding In no case was a disturbance in the flow of impulses from the implanted pacemaker followed immediately by Adams-Stokes seizures, because the patient s own pacemaker invariably took over Proper adjustments were made by exchange of the pacemaker and wire electrodes.

A postcardiotomy syndrome was observed in 3 of 21 surviving patients. The complication is annoying because of pain and a tendency to recurrence but it entails no serious danger to life.

3 Favorable results Among the surviving 21 patients the pacemaker worked successfully in 19 over periods of observation which ranged from 2 to 19 months (Table I) In the other 2 patients who had recovered normal sinus rhythm or idioventricular rhythm after implantation of the pacemaker no attempt was made to implant a new pacemaker after breakage of the wires in the original one Once a pacemaker was implanted Adams-Stokes seizures vanished Particularly striking wa

the disappearance of the ventricular tachyarrhythmias as soon as fixed bradycardia was replaced by the faster electrical rhythm. However, in one patient in whom fainting spells were caused by ventricular flutter-fibrillation in the absence of heart block, no significant change resulted from implantation of a pacemaker.

Congestive heart failure was present in more than half of our patients prior to implantation of the pacemaker. The adverse effect of fixed bradycardia on hemodynamic conditions and, on the other hand, the increase in the cardiac output after acceleration of the heart rate by electrical stimulation have been studied in the experimental animal and in man.[8-] Our own clinical observations are in agreement with those of others. An increase in heart rate does not, as a rule, cure congestive heart failure but brings about symptomatic improvement. This was particularly striking in one patient who had suffered from severe congestive heart failure. After implantation of the pacemaker he tolerated more strenuous activities by increasing the rate of formation of electrical stimuli through application of an external control unit which accelerated the rate of stimulation. On the other hand, failure of the pacemaker which brought his heart rate suddenly down to the low pace of his idioventricular center (40 per minute or less) was accompanied by marked respiratory distress.

Indications for long-term use. The indications for long-term use of an implanted pacemaker are not yet fully determined. The employment of a pacemaker is imperative when (a) surgical repair of a congenital septal defect results in heart block with bradycardia which does not yield a cardiac output sufficient for postoperative needs,[2] and (b) in instances of syncopal attacks due to ventricular flutter-fibrillation which more often than not entail serious danger to life. In these cases an artificial pacemaker should be supplied without delay. As a rule, a pacemaker rate of 60 per minute is sufficient to prevent recurrence of tachyarrhythmias. However, in two instances, during the immediate postoperative period, the pacemaker rate had to be increased to 80 per minute in order to prevent the recurrence of seizures.

The indication is less well defined in the presence of Adams-Stokes seizures which are caused by ventricular standstill. In such instances it is a good policy to exhaust first all the available means of medical therapy before operation is contemplated. When syncopal attacks occur in great frequency or have a tendency to recur, endangering the life of the patient, surgical implantation of a pacemaker is justified. Occasionally, however, this measure must be considered even in less desperate cases, for instance, when syncopal attacks have caused a profound emotional disturbance, a feeling of anxiety, so that the patient is afraid to walk in the street or to stay at home alone, being ever conscious of the danger of falling unconscious. Surgical intervention may then be desired even in the face of a risk involved when submitting to operation. Likewise, when heart block is associated with chronic congestive heart failure which does not yield to ordinary medical treatment, one might sometimes feel justified in making an attempt to influence the condition by accelerating the heart rate through artificial stimulation.

Table I. Length of observation time in patients successfully paced by implanted pacemaker

Months	Number of patients
1-3	2
3-6	3
6-12	6
12-18	6
18-20	2
	Total 19

Summary

Twenty-seven patients were treated in the Maimonides Hospital with implanted pacemakers. The indications were: heart block with bradycardia and recurrent syncopal attacks and especially syncopal seizures caused by ventricular flutter-fibrillation. In one instance congestive heart failure with fixed bradycardia was the chief indication.

Stimulation by way of catheter electrodes was employed in most instances temporarily prior to implantation of the pacemaker.

There were 6 fatalities of which only one was indirectly related to failure of the pacemaker. The others were due to postoperative coronary attacks, congestive heart failure, bacterial endocarditis or intestinal bleeding.

Disturbances in the pacemaker circuit occurred in 6 instances, and were due mainly to breaking of electrode wires or slipping of electrodes. Invariably the patient's own pacemaker took over until the disturbance was remedied. In the surviving patients the results were excellent in instances of Adams-Stokes syndrome and especially gratifying when syncopal attacks were caused by tachyarrhythmias. In the presence of congestive heart failure symptomatic improvement was observed.

The indications for implantation of a cardiac pacemaker are discussed. In the immediate postoperative period a pacemaker rate of 60 per minute may be inadequate to prevent the recurrence of ventricular flutter fibrillation.

Addendum

Since this paper was completed the number of patients in whom a pacemaker was implanted rose to 33. An 83-year-old patient who was operated upon because of Adams-Stokes seizures due to tachyarrhythmias died on the ninth postoperative day of ventricular flutter fibrillation. The attack, which was recorded electrocardiographically, developed while the pacemaker functioned well at a rate of 60. In 2 other patients the pacemaker had to be exchanged because of exhaustion of the batteries after undisturbed function for 17 and 21 months, respectively. On the other hand, for the past 6 months we were using a new type of electrode. So far no breakage of the electrode wires has been observed.

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Bundle branch block on cardiac slowing at a critical slow heart rate

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Aberration or bundle branch block which occurs as a critical heart rate is exceeded is well known and not uncommon.[1-4] Its occurrence on cardiac slowing at a slow rate is extremely rare. We have been able to find only 2 acceptable cases and 2 other possible cases reported previously. The purpose of this paper is to briefly mention these 4 cases from the literature, add 2 new ones, one of them with a conduction disturbance heretofore undescribed, and to discuss the possible physiologic mechanisms.

The first acceptable case reported (1941) was that of a 50-year-old woman with previous hyperthyroidism, arteriosclerotic heart disease, atrial fibrillation, and bradycardia. She had not received digitalis before the electrocardiograms were taken. The critical ventricular rate was 40.3 per minute. Whenever the rate slowed to this or less, bundle branch block ensued; when the rate increased to above this, the QRS duration was normal. It varied from 0.07 to 0.12 second. The change from normal to block, or the reverse, usually took place within the period of one cycle. Of 83 QRS complexes† in a single tracing, 36 were normal in duration and 47 were wide. There were 22 changes back and forth between QRS waves of normal duration and those of bundle branch block.

In 1959 Dressler[1] described the case of a 57-year-old woman with hypertensive and arteriosclerotic heart disease and sinus bradycardia. The heart rate was 40.5 to 53.5 per minute, and the critical rate was 43.4, with bundle branch block when the rate was slower (17 complexes) and QRS of normal duration in 136. The aberrant ventricular complexes occurred only after long cycles which showed marked and usually abrupt increments in duration, 0.10 to 0.38 second. Both slowing and conduction disturbances were attributed to increased vagal tone.

In the report of Comeau, Hamilton, and White, their Case 8 was that of a patient with hypertensive and coronary artery disease and pulmonary congestion who had been receiving digitalis. During carotid sinus pressure with slowing of the heart rate to between 30 and 40 per minute, 2 isolated beats occurred, each with a wide QRS (0.16 second) and a normal P-R interval (0.18 second). The authors stated that they believed that these 2 beats represented bundle branch block and not ventricular escape. These 2 ventricular complexes were similar to those present on another date when there was ordinary bundle branch block at a rate of 79 to 108. Because only 2 beats were involved, the case is not reported here in greater

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†Only those QRS complexes at the end of complete R-R cycles were included in the analyses in this paper.

detail but the comments in regard to vagal tone possibly concerned are referred to later.

A case reported by Holzmann (1943) was of much interest and was considered by him to be the first reported of the "paradoxical" occurrence of bundle branch block with slowing due to the bradycardic phase of a respiratory arrhythmia. This case is mentioned only as a possible case in the present report because the control QRS was abnormally wide (0.14 second, which he called "pathologic left type"); the QRS interval during bundle branch block was 0.21 second.

New Case 1. This patient, a 76-year-old man with an acute respiratory infection, had arteriosclerotic heart disease, marked cardiac enlargement, especially of the left ventricle, atrial fibrillation, bradycardia, and considerable heart failure. Râles were heard over the dependent lung base, the liver was moderately enlarged, and there was slight ankle edema. The antecubital venous pressure was 180 mm. of physiologic saline, and the Decholin arm-to-tongue circulation time was 24 seconds. The blood pressure was 140/96 mm. Hg. Urinalysis and hemogram were not remarkable. Blood chemistries—sugar, urea nitrogen, albumin and globulin, sodium, potassium, chlorides, CO_2, and bilirubin—were normal. The electrocardiogram taken on Dec. 7, 1961, showed a pattern of left ventricular hypertrophy, atrial fibrillation, and bradycardia (Fig. 1). The QRS was 0.09 second and of large amplitude in the precordial leads. S in Lead V_1 or V_2 plus R in Lead V_5 or V_6 was 46 mm., and the mean QRS vector was directed along the minus 10° axis in the frontal reference frame. One hundred and eleven ventricular cycles were recorded. The duration of QRS was normal in 79 and increased in 32. There were 43 changes from normal to aberrant, or from aberrant to normal, 7 with 2 to 4 consecutive wide complexes. The aberrant complexes were 0.13 to 0.14 second with a prominent wide terminal S in Lead I (0.06 to 0.07 second) and a qR in Lead V_1, with the intrinsicoid deflection time (to R peak) 0.08 second. Over the left side of the precordium qRS was recorded; the S was 0.05 second and the intrinsicoid deflection time was only 0.045 second, conforming to the pattern of right bundle branch block.

The duration of cycles which preceded normal QRS complexes was 1.02 to 1.71 seconds, mean 1.39 seconds; the duration of cycles which preceded the bundle branch block complexes was 1.72 to 1.80 seconds, mean 1.74. The critical rate was 35.0 beats per minute (R-R, 1.71 to 1.72 seconds). Thus, at a rate of 35.1 beats per minute, intraventricular conduction time was normal, and at a rate of 34.9, bundle branch block was present, a difference in rate of only 0.2 beat per minute between conduction and nonconduction in the right bundle branch.

The electrocardiogram was repeated 3 days later with similar findings. Sixty-eight cardiac cycles were recorded, with the normal type of ventricular complex in 35, bundle branch block configuration in 25, transitional complexes in 7, and 1 apparent ectopic beat.* There were 35 changes from normal to aberrant or from aberrant to normal QRS complexes. The duration of the cycles which preceded normal QRS deflections was 1.08 to 1.69 seconds, mean 1.46; the duration of those which preceded wide QRS waves was 1.62 to 1.88, mean 1.73 seconds. The critical rate in the tracing of that day was 36.3 beats per minute (R-R, 1.65 seconds). In two instances (*not illustrated*) when there was a large and sudden increase or decrease in rate between one beat and the next, the critical rate level was altered slightly (0.02 to 0.04 sec.) compared to periods with small gradual changes in rate.

*An alternative interpretation of this electrocardiogram may be atrial fibrillation and transient complete heart block with idioventricular rhythm. The diagnosis of bundle branch block occurring at a critical heart rate was indicated by the following features. (1) The occurrence of aberrant ventricular complexes of the right bundle branch block type whenever the rate became slower than the critical rate. (2) Similarity in circumstances—bundle branch block on cardiac slowing at a critical rate—to cases in the report with sinus rhythm, in which transient complete A-V heart block is almost certainly not occurring. In one case (see later) a P wave with a constant P-R interval precedes each of the 25 aberrant QRS complexes which strongly suggest that A-V conduction is occurring, and that the wide QRS complexes represent bundle branch block rather than ventricular escape beats. (3) Variable configuration of the aberrant ventricular complexes apparently due to transitional complexes (T in Fig. 1,B); also, a sequence of 3 consecutive QRS complexes with progressively increasing aberration due to transitional complexes was recorded. (4) Considerable variation in cycle length for the aberrant complexes, with differences up to 0.4 second.

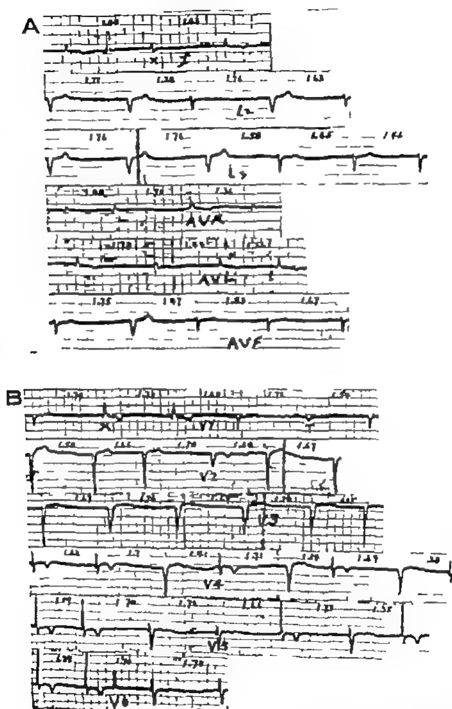


Fig. 1. New Case 1. Combined electrocardiogram showing bundle branch block on cardiac slowing t critical heart rate. Leads II, III, \ \ \ \ and \ are from tracing taken on Dec. 7, 1961 critical rat was 35 beats per minut (R R, 1.71 seconds). Leads I, \ \ and \ are from tracing taken on Dec. 10, 1961 the critical rate was 36.3 (R R, 1.65 seconds). The combined 12-lead illustration taken from te tracings (Dec. 7 and Dec. 10) was used for display of more fluctuations in conduction. Time in seconds is recorded over cycles. X, Aberrant beats at end of cycles of *1.72 to 1.88* seconds. *T*, Transitional entricular complex. *A*, Limb leads. *B*, Precordial leads. Consult text for details.

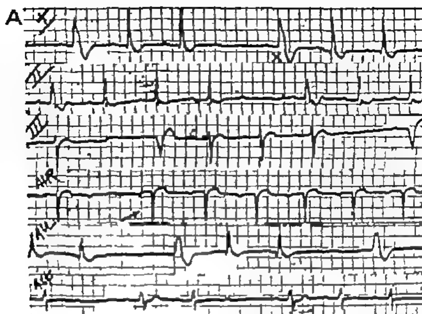


Fig. 2. New Case 2. Electrocardiogram showing bundle branch block on cardiac slowing due to blocked ventricular beats in intermittent partial A-V heart block. Critical rate between 33.7 and 33.1 beats per minute (R-R 1.78 to 1.81 seconds). When the rate was only slightly faster, 33.7 beats per minute (R-R, 1.78 seconds), bundle branch block failed to develop (second QRS in aVR, arrow). A, Limb leads. B, Precordial leads V and V, one-half standardization. Consult text for details. (For B see opposite page.)

During the taking of the third electrocardiogram on this patient (Dec. 14, 1961) respiratory maneuvers and carotid sinus pressure were carried out. In this tracing there were 80 cardiac cycles, 65 with normal QRS complexes and 15 with bundle branch block; the latter included runs of 2 to 4 consecutive aberrant complexes. Eighteen changes between normal and wide QRS deflections occurred. The duration of the cycles which preceded normal QRS waves was 1.04 to 1.56 seconds, mean 1.32 seconds; the duration of those which preceded bundle branch block complexes was 1.60 to 1.715 second, mean 1.64 seconds. The critical rate was between 37.5 and 38.5 beats per minute. During deep inspiration 2 cycles, 1.62 and 1.64 seconds, had QRS deflections of normal width; during deep expiration 1 cycle at 1.47 seconds had a bundle branch block complex. During the application of carotid sinus pressure the ventricular rate was not reduced to below the critical level. All QRS waves were of normal width.

In the 3 tracings a total of 259 cycles was recorded, 179 with normal QRS complexes and 79 with bundle branch block type with runs of the latter of 4 or more consecutive beats. There were 96 changes between normal QRS complexes and those of the bundle branch block type. The critical cardiac rates on the 3 days were 35, 36.3, and 38 beats per minute.

New Case 2. The patient, a 63-year-old white man, had advanced hypertensive and arteriosclerotic heart disease with both left-sided and right-sided heart failure. He had been digitalized and was receiving 0.25 mg. of digoxin daily. An electrocardiogram taken on Jan. 13, 1960 (Fig. 2), showed sinus rhythm with an atrial rate of 62 per minute. P-R intervals were 0.27 to 0.36 second. There was second-degree partial A-V heart block, at times 3 to 2, and occasional Wenckebach periods. The regular QRS interval was 0.09 second. The mean QRS vector was directed along the minus 7° axis of the frontal reference frame. S in Lead V_1 plus R in Lead V_5 was 66 mm., which was suggestive of the presence of left ventricular hypertrophy. RS-T was depressed in Leads I, II, aV_L, V_4, V_6, and

*This case is included through the kindness of Dr. N. Shafer.

V₄, and Q-T was 0.33 second which was suggestive of digitalis effects.

One hundred and two cardiac cycles were recorded 73 between 0.92 and 0.99 second each with QRS deflections of normal width. There were 29 long cycles each due to a blocked ventricular beat and measuring 1.81 to 1.93 seconds, with one exception at 1.78 seconds (Fig. 2, *arrow* Lead aV$_R$). In all the long cycles, exclusive of the one exception the QRS which immediately followed a blocked ventricular beat was abnormally wide 0.14 second and conformed to the pattern of complete left bundle branch block with the T waves in a direction opposite to the major QRS deflection (Fig. 2 X). The exceptional cycle at 1.78 seconds was the only one of the 29 long diastoles each due to a blocked ventricular beat which was not immediately followed by a bundle branch block complex but by a QRS of normal duration (Fig. 2, *arrow*) and identical in form to the regular ventricular complexes of the tracing. This would indicate that slowing of the ventricular rate to between 33.15 and 31.09 beats per minute (R-R, 1.81 to 1.93 seconds) in this setting was able to induce bundle branch block, but that slightly less slowing that is, to 33.7 (R-R, 1.78 seconds) was not able to do so. The critical rate was between 33.7 and 33.15 beats per minute (R-R 1.78 to 1.81 seconds). Most of the 29 long diastoles were part of the Hay type of partial A-V block, with the P-R intervals at each end of a long cycle equal and about 0.32 second. Several long cycles, however were part of Wenckebach periods with varying P-R intervals.

Five days later (Jan. 18 1960) the electrocardiogram (*not illustrated*) showed complete 1:1 bundle branch block during the entire record. The ventricular complexes were similar to the 28 wide QRS complexes of Jan. 13 1960 which had occurred only at the end of the very long cycles, 1.81 to

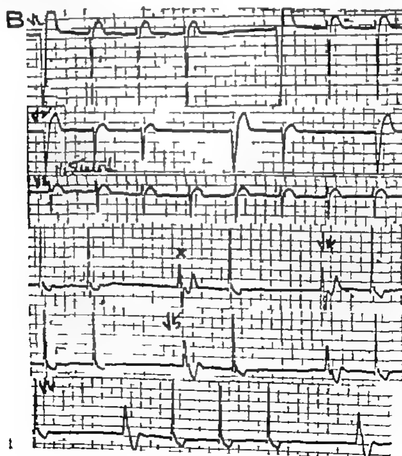


Fig. 2.B (For legend see opposite page.)

1.93 seconds. The heart rate was 77, the P-R interval was 0.28 second, and the QRS duration was 0.14 second. The aberrant ventricular complexes in Lead aVR were strikingly different from the QRS in Lead aVR in Fig. 2 (a, arrow).

Discussion

The occurrence of aberration or bundle branch block when a critical heart rate is exceeded is readily explained in accordance with well-established principles of electrophysiology for conduction in cardiac tissues. A supraventricular impulse arriving at a bundle branch during its phase of partial or complete refractoriness pursues a delayed and supposedly anomalous course in the homolateral ventricle. At very rapid rates this may be a normal functional phenomenon—aberration right sided in 85 per cent, the result of "fatigue" due to a short diastolic period for physicochemical recovery. At less rapid heart rates such aberrant ventricular conduction is due to refractoriness which is abnormally long and is regarded as intraventricular or bundle branch block. Conduction by preferential pathways may have to be considered in certain instances. Delayed conduction or block has been demonstrated in individual fibers of the bundle branches as well as in other specialized cardiac conduction tissues.

Aberration or bundle branch block which occurs at slow heart rates on further slowing and which is exemplified in the above-described cases is more difficult to explain. Several possibilities may be considered.

Circulatory and functional. There is a comparative paucity of data on the effects of very slow heart rates on refractoriness of cardiac tissues. One of the reasons is the difficulty of setting up in normal live hearts experimentally slow heart rates which are very much slower than the normal.[19] In general, the length of the refractory phase varys with the length of the cycle: longer cycles have longer refractory periods whose lengths also vary in curvilinear fashion with the length of the immediately preceding cycle.[19,20] Carmeliet,[8] using strips of frog ventricle, found that the duration of the action potential at a given rate approaches the duration at infinitely slow rates (A ∞ in his formula) asymptotically, with little or no change in duration at rates below 50 per minute. A ∞ was affected by the physiologic state. Hoffman and associates,[17,21] employing electrodes chronically implanted over parts of the specialized conduction system, indicated a good correspondence between the duration of the transmembrane action potention and the duration of refractoriness from the same fibers in the intact dog heart. This relationship may be changed by a local response factor[1] by various agents, such as low temperature, metabolic inhibition, altered pH, and drugs.[8] Hoffman and Suckling demonstrated a linear correlation between the total duration of the action potential (mainly Phase 2) and rate—from 60 to 300 per minute. Below 50 per minute the duration of Phase 2 was constant.[22,24] At infinitely slow rates the duration of the action potential may be over three times that when the rate is rapid.[22] They believed that beyond a certain limit of slowing in any particular cardiac cell the duration of the action potential at such a slow rate is presumably determined solely by the general environmental factors, temperature, and ionic milieu acting in conjunction with whatever mechanisms are responsible for repolarization.[22] Decremental conduction has not been established for normal bundle branch tissues, but is suspected in damaged tissues.[12,21] It appears to occur in the normal A-V node (N zone).[22] Bundle branch tissues were found to be quite sensitive to ischemia, although they were not so sensitive as were ventricular muscle cells. Retained metabolites, changes in blood pH and electrolyte, and other factors have been suggested as perhaps playing a greater role (than does hypoxia) during ischemia, and these factors need further study.[22]

In general, as the length of the cycle gets longer, repolarization and recovery of excitability improves, and the later an impulse arrives in the cardiac cycle, the better are the opportunities for its transmission. At slow rates then its impaired conduction cannot be attributed to action of the normal refractory period when one considers the long cycle of these beats. Likewise, latent intraventricular conduc-

tion defects usually may not be invoked in such cases. However with a sufficient degree of slowing during the long pauses between beats, especially in the presence of severe coronary artery disease coronary blood flow may be decreased with further ischemia of cardiac tissues, including the specialized tissues (the bundle branches, etc.) Such reduced blood supply with possible resultant local metabolic inhibition hemodynamic and physicochemical changes and alteration in the transmembrane ionic gradient could be responsible for impaired conduction there, which is not present at rates less slow This hypothesis may explain some instances of bundle branch block brought on by sufficient slowing at an already slow heart rate. In greater or lesser degree it may apply to all 6 cases mentioned above particularly to the second old[7] and the second new cases (Fig 2) in which other possible causes are not apparent. The need for further experimental studies on local circulatory changes brought on by slowing of the heart rate at slow rates, and their effect on conduction in the specialized tissues of the heart, is obvious.

Vagal effects Recent anatomic,[24,25] experimental[26] and clinical studies[27] have indicated the possibility of direct vagal influence on the ventricles—long denied although early suggested by Lewis,[29] Wilson[28] and others. In intermittent bundle branch block the usual effect of vagal stimulation is to induce normal intraventricular conduction which is attributed most often to an indirect action—slowing of the heart rate. Comeau Hamilton and White, in their case previously referred to with bundle branch block in 2 isolated beats on slowing of the heart rate by carotid sinus pressure considered this to be evidence that the vagus may exert a direct influence on conduction in the bundle branches. They did state that their experience and published data showed that an increase in vagal tone does not produce sustained inhibition of bundle branch conduction—only by an effect on heart rate

Holzmann in the report of his case mentioned above in which slowing of the heart rate at a slow critical level was associated with an increase in QRS interval from 0 14 to 0 21 second believed that this was due to a direct effect of the vagus on a bundle branch as yet undetermined. He suggested the possibility that *Vagusstoff* was produced in more cranial parts of the heart, the acetylcholine then flowing down to the ventricle localized disease possibly making the bundle branch tissue more sensitive to vagal impulses. This explanation does not appear to be in accord with newer concepts of the mechanism of action of acetylcholine on conduction in nerve and cardiac muscle.[29] Dressler suggested that in his case described above,[3] the induction of bundle branch block on cardiac slowing was an effect of the increase in vagal tone and thought of the possibility that this might act by causing coronary vasoconstriction—an admittedly controversial opinion [3,24,31]

Wallace and Laszlo[32] in an extensive study of a case of intermittent bundle branch block, recorded the effects of respiratory maneuvers, carotid sinus pressure, and drugs, including the use of oxygen and carbon dioxide. They obtained both termination and induction of left bundle branch block with carotid sinus pressure—related to the force applied to the sinus. Among the various observations in this case was much overlapping in heart rates during conduction and block, and they believed that they did not know which factors were most important in governing the modes of intraventricular conduction

In studies of single fibers, Hoffman and Cranefield[11,33] found that ventricular and Purkinje fibers were extremely insensitive to the action of acetylcholine and vagal stimulation although the A V node, especially the part adjacent to the atrium was quite sensitive. Further clarification of the nature of the direct vagal effect, if any on bundle branches would be desirable

Concealed conduction Concealed conduction has been shown to be a common occurrence in all three specialized cardiac tissues.[11,34] In studies of single fibers, concealed conduction of atrial activity has been demonstrated to extend as far as the peripheral Purkinje fibers. Because of its action block may occur between the bundle of His and bundle branches or be-

tween the bundle branches and Purkinje fibers.[1] It is conceivable, therefore, that under suitable local settings of circulatory, metabolic, neural, and ionic alterations a supraventricular impulse during atrial fibrillation may penetrate up to but not be transmitted completely through a main bundle branch. This concealed conduction might affect the next transmitted impulse and be responsible for its partial or complete blockage at this site—the bundle branch. Thus concealed conduction is an attractive explanation for the occurrence of bundle branch block with slowing of the ventricular rate during atrial fibrillation as in New Case 1 (Fig. 1). This need not preclude circulatory changes (without concealed conduction) as the cause in some such cases with atrial fibrillation.

In New Case 2 (Fig. 2) it may be suggested that concealed conduction was present during the periods of partial A-V block, that the atrial impulse penetrated the A-V node, the main bundle, and left bundle branch, but without further transmission. This would not seem to be an adequate explanation of the bundle branch block in the following ventricular complex (Fig. 2, A) since intraventricular block did not occur in the regular beats, with short cycles, or in the beat with A-V block and an R-R period of 1.78 seconds (Fig. 2, arrow).

Auxomerous conduction. An anatomic and physiologic condition peculiar to cardiac tissues which may be concerned with unstable bundle branch conduction at a critical heart rate and fluctuations between conduction and block on slightest alterations[25,27] such as a slight change in heart rate is auxomerous conduction. The smallest portion of the bundle if undivided can carry all the conduction.[25,27] The smallest number of fibers needed is unknown. This type of conduction is enhanced because of the syncytial nature of cardiac muscle tissue. Branching has been demonstrated in the bundle of His and peripherally.[7] The possible long duration of the condition of unstable conduction in a bundle branch—10½ years in one case[1]—seems to be more understandable on the basis of auxomerous conduction in addition to other factors mentioned above.

Conclusion

The clinical occurrence of aberration or bundle branch block on slowing of the heart rate at slow rates appears to be quite definite and related to the changes in rate. The explanations offered for the mechanism of occurrence—on a basis of circulatory changes or vagal effects or concealed conduction and auxomeric conduction—are hypotheses which require confirmation and further elucidation.

Summary

Aberration or bundle branch block on cardiac slowing at a critical slow cardiac rate is discussed. Only 4 illustrative cases were found reported in the literature and these were mentioned briefly. Two new cases were added and described in detail. Reported for the first time was an instance of transient bundle branch block which was apparently induced by cardiac slowing caused by intermittent partial A-V heart block with a critical heart rate.

Explanations for the occurrence of aberration or bundle branch block on cardiac slowing at slow heart rates were considered. Possible circulatory and physicochemical changes and vagal effects were discussed. Concealed conduction and auxomeric conduction were also considered. Pertinent reported electrophysiologic and clinical studies on conduction and refractoriness in bundle branch tissues which were possibly concerned with the electrocardiographic phenomena observed on cardiac slowing in the cases described were reviewed. Possible mechanisms of occurrence of aberration or bundle branch block on cardiac slowing at a slow heart rate were suggested.

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The electrocardiogram in infarction of the anterolateral papillary muscle

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Myocardial infarction which involves the papillary muscles has received little attention from either the standpoint of electrocardiography or from the standpoint of altered mechanical function. During the last few years, several patients with significant apical systolic murmurs without evidence of the usual causes of such murmurs have been seen. At autopsy these patients have frequently shown moderate to extensive infarction of the left ventricular anterolateral papillary muscle with no other anatomic lesions to explain the murmur which had been detected during life. Subsequently, evidence was accumulated which supported the existence of an entity of mechanical dysfunction of the papillary muscle.[1] Therefore it was of obvious importance to be able to recognize the presence of this lesion during life, and the electrocardiogram was considered to be a major parameter worthy of careful study. Previous experience with a continuing program at this institution over several years of clinical and necropsy correlation had left an impression that anterolateral papillary muscle infarction could be suspected from electrocardiographic changes. These changes seemed to fall into three major groups. The first group (Type I) consisted of moderate to marked depression of junction J in the middle and left precordial leads associated with a concavity-upward deformity of the ST-T interval (Figs. 1 and 2). The second group (Type II) consisted of changes in the middle and left precordial leads with, however, slight depression of junction J and a convexity-upward deformity of the ST-T interval and terminal inversion of the T wave (Fig. 3). The third group consisted of changes in these same leads with, however, an extremely marked depression of junction J associated usually with slight initial convexity-upward deformity of the ST-T interval (Fig. 4). The present preliminary study was undertaken in an attempt to determine the reliability of these changes in predicting significant infarction of the anterolateral papillary muscle.

Methods

The electrocardiographic files and pathology records of all patients autopsied at the New Orleans Veterans Administration Hospital from Jan. 1, 1962, through Nov. 1, 1962, were carefully reviewed. All clinical records of patients whose electrocardiograms were interpreted as being suggestive

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of anterolateral papillary muscle infarction were studied (23 patients). Likewise all autopsy records of patients in whom papillary muscle infarction was found were collected for study (21 patients). One patient who showed papillary muscle infarction at autopsy was excluded from the study since all of the electrocardiograms recorded prior to death had shown left bundle branch block.

Results

There was a good correlation between the electrocardiographic changes and the autopsy findings. Of 21 patients noted at autopsy to have infarction of the anterolateral papillary muscle 20 (95 per cent) had electrocardiograms which were interpreted as being strongly suggestive of this lesion. The importance of such an excellent correlation is uncertain since

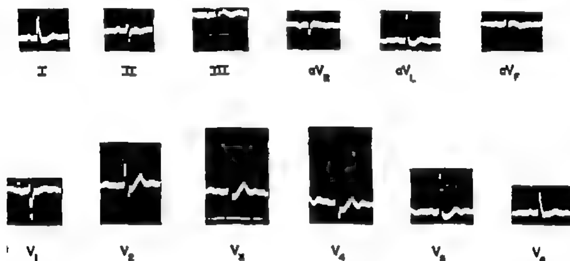


Fig. 1. Type I anterolateral papillary muscle infarction characterized by concavity-upward deformity of the ST-T interval. The depression of junction J, concavity-upward deformity of the ST-T interval, and T-U segment depression are displayed best in Leads V and V. (Patient E.S., age 67, white male.)

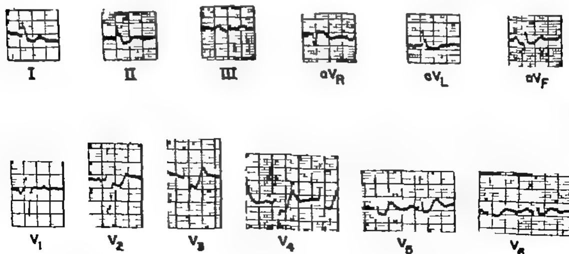


Fig. 2. Anterolateral papillary muscle infarction, Type I. The depression of junction J, concavity-upward deformity of the ST-T interval and U-wave inversion are displayed best in Leads V through V. (Patient J.G., age 74, white male.)

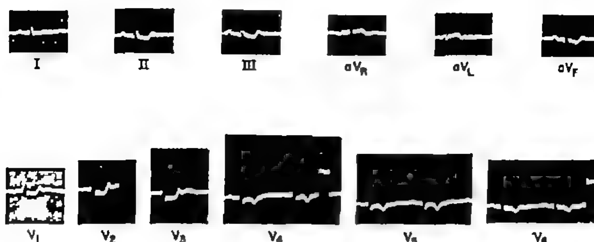


Fig. 3. Type II anterolateral papillary muscle infarction characterized by concavity-upward deformity of the ST-T interval, J junction depression, convexity-upward deformity of the ST-T interval, T-wave inversion and shallow Q ... of the ... are displayed best in Lead V through V. (Patient S.N., age 31, white male.)

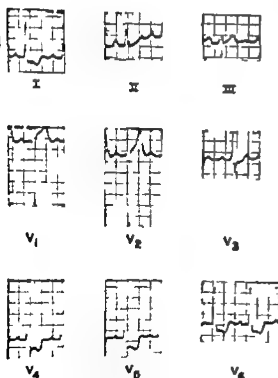


Fig. 4. Anterolateral papillary muscle infarction, Type III, characterized by very marked depression of junction J. Depression of junction J, slight ... convexity-upward deformity of the initial ST-T interval, and shallow T-wave inversion are displayed best in Lead V through V. (Patient G.W., age 65, white male.)

undoubtedly the electrocardiographic interpretation influenced to a large degree the care and thoroughness with which the papillary muscles were examined pathologically. However, it should be noted that the papillary muscle infarcts found in this series of patients usually involved a large area of the papillary muscle and generally were quite easy to recognize (Fig. 5). Nevertheless, from the electrocardiographic standpoint the incidence of false-negative interpretations cannot be accurately determined. Likewise, the true incidence of papillary muscle infarction in the autopsy population of this institution was not investigated.

Of 23 patients who were suspected electrocardiographically of having anterolateral papillary muscle infarction, confirmation was made at autopsy in the above-mentioned 20 (87 per cent). Thus, in these patients the incidence of false-positive interpretations was 13 per cent (3 patients). Of the 3 patients in whom false-positive interpretations were made, one showed marked digitalis effects on the electrocardiogram and right and left ventricular hypertrophy at autopsy, another had left ventricular hypertrophy and diffuse myocardial scarring at autopsy, and the third had electrolyte imbalance (hypokalemia) and digitalis effects electrocardiographically and showed right and left ventricular hyper-

trophy and marked apical scarring at autopsy

It is worth noting that, although the electrocardiographic interpretation of papillary muscle infarction was not dependent upon it, most of the records studied demonstrated clear-cut abnormalities in the T U segment and U wave area. These usually consisted of T U depression or U wave inversion in the left precordial leads. Indeed these changes may prove to be reliable evidence of papillary muscle ischemia and/or infarction

Discussion

This study demonstrates that infarction of the left ventricular anterolateral papillary muscle can be reliably predicted from the electrocardiogram In this group of patients the accuracy of the prediction was 87 per cent Most of the records studied appeared to fall generally into one of three groups (Types I II or III) but some had characteristics which fell into more than one group depending on the specific precordial lead studied The interrelationships of these groups and the evolution of these electrocardiographic changes are presently being investigated



Fig 3 Heart of Patient E.S whose electrocardiogram is shown in Fig. 1. There is large infarct of the anterolateral papillary muscle (arrow).

In the 13 per cent of the instances in which the electrocardiogram was falsely positive for this lesion other complicating factors known to influence the electrical activity of the heart were present The electrocardiographic findings described are not specific since one or more of the following conditions alone or especially in combination could lead to difficulty in interpretation left ventricular hypertrophy the shock syndrome (especially if treated with potent vasopressors) subendocardial infarction or hemorrhage not necessarily involving the papillary muscle digitalis effects, posterior-diaphragmatic transmural myocardial infarction post tachycardia syndrome coronary insufficiency severe intraventricular conduction disturbances, and electrolyte imbalance However in the patients studied many of these factors were occasionally present but electrocardiographic interpretation was still accurate However there is little doubt that the conditions mentioned above can result in false positive electrocardiographic interpretations of papillary muscle infarction Detailed studies to delineate the contribution of such factors in the presence of papillary muscle infarction are presently in progress. Furthermore, at present, it is not known whether isolated infarction of the left ventricular posteromedial papillary muscle can produce the electrocardiographic changes described in the absence of involvement of the anterolateral muscle.

The presence of apparent T U segment depression and U wave inversion in the majority of electrocardiograms of patients with papillary muscle infarction is of interest. The significance of these changes in light of some evidence relating U wave potential to repolarization of the papillary muscles remains to be clarified.

Summary

An electrocardiographic syndrome has been described which allows fairly reliable prediction of the presence of infarction of the left ventricular anterolateral papillary muscle. The changes in the electrocardiogram generally fall into three major groups. One consists of moderate to marked depression of junction J in the middle and left precordial leads associated with a concavity-upward deformity of the ST T

interval. Another consists of changes in the same leads with, however, slight depression of junction J and a convexity-upward deformity of the ST-T interval and terminal inversion of the T wave. The third consists of changes in these leads with, however, an extremely marked depression of junction J associated usually with slight initial convexity-upward deformity of the ST-T interval. The presence of apparent T-U segment depression or U wave inversion was detectable in the majority of electrocardiograms in all three groups.

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Experimental and laboratory reports

A study of retrograde pressure and pulse in the sinus node artery

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During the course of investigations utilizing direct perfusion of the sinus node through its own artery,[1-3] we noted that a pulsatile pressure of considerable magnitude was present in this artery, the origin of which had been ligated. This report concerns studies performed to determine the source of this retrograde pressure and pulse.

Method

In 37 dogs anesthetized with intraperitoneal pentobarbital (30 mg. per kilogram) the heart was exposed with a sternal-splitting incision and the trachea was intubated for mechanical ventilation. A small polyethylene cannula was inserted into the right coronary artery near the margo acutus and passed up the sinus node branch in a manner previously described. Placement of the catheter required ligation of the distal third of the right coronary artery, so that there was no antegrade flow into the sinus node branch via its usual route.

It had previously been determined that ligation of all the visible blood supply of the canine sinus node had no significant effect on sinus rhythm in the course of acute experiments which lasted several



Fig. 1. A postmortem angiogram of the experimental model used in these studies. The small polyethylene cannula is wedged in the sinus node artery, which is seen opacified beyond the tip of the cannula (*lower arrow*). The artery passes through the sinus node at the point indicated by the upper arrow and may be seen continuing for a distance up the superior vena cava, which is supported by the upper clamp.

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hours. After ligation of the sinus node artery routes of collateral circulation to the sinus node are multiple and apparently copious in flow. Arteries which normally contribute to this collateral circulation to the node include the anterior left atrial artery and the anterior and intermediate right atrial arteries[4] but the most important single collateral arterial source is a large artery which descends on the superior vena cava (Fig 1). It is significant that the sinus node artery does not terminate in the node but passes directly through it as a major artery both in man[1,4] and the dog.[1,7]

To record retrograde pressure and pulse in the sinus node artery a transducer was connected to the shank of the cannula in the artery. Simultaneous pressures were recorded in the right atrium and central aorta and a simultaneous electrocardio-

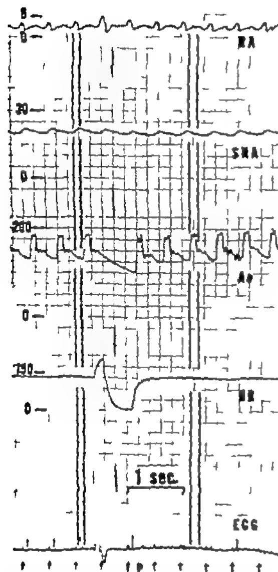


Fig. 2. A simultaneous recording (*from above down*) of right atrial pressure, sinus node arterial pressure, central aortic pressure, heart rate (from a tachometer) and the electrocardiogram. The vertical intercepts facilitate identification of the relationship of the onset and peak of the sinus node arterial retrograde pulse (*first two vertical* [illegible]) to other measurements, and of the onset and dicrotic notch of the central aortic pulse (*second two vertical* [illegible]). The ventricular premature beat produces no [illegible] aortic pulse nor does it interfere with atrial contraction, which does produce a pulse in the sinus node artery. P waves are indicated by the lowermost row of arrows. The scale of pressures is in millimeters of mercury.

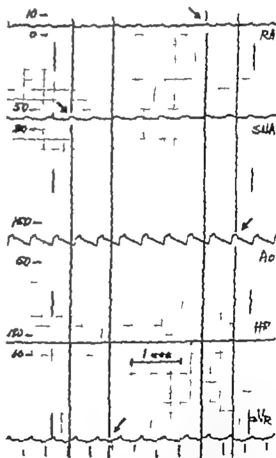


Fig. 3. The retrograde pulse in the sinus node artery of a second dog recorded in a manner similar to that in Fig. 2. The four arrows [illegible] the complex which is being related to simultaneous other phenomena. From the left they point to the peak of sinus node arterial pulse, nadir of the [illegible] peak of the right atrial [illegible] and the approximate peak of the central aortic pulse.



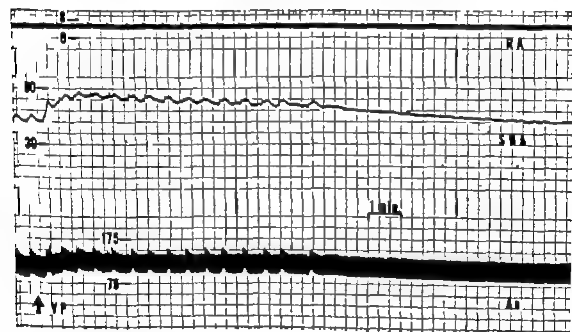


Fig 4 *Above* Simultaneous recording of central aortic and retrograde sinus node arterial pressures after the intravenous injection of norepinephrine 0.01 mg per kilogram in 10-kilogram dog *Below* Similar record after intravenous vasopressin 0 1 unit per kilogram.

gram completed the routine determinations. In 6 dogs, retrograde pressures and pulses were determined from ventricular branches of the right and left coronary arteries and recorded simultaneously with those from the sinus node artery In 2 dogs the right intermediate atrial artery supplied the same area of atrial myocardium as did the normal sinus node artery but did not supply the node as determined by lack of nodal response to a test injection of 1 0 μg of acetylcholine (0 1 to 0.3 μg ordinarily arrests the sinus node when injected into the sinus node artery) The retrograde

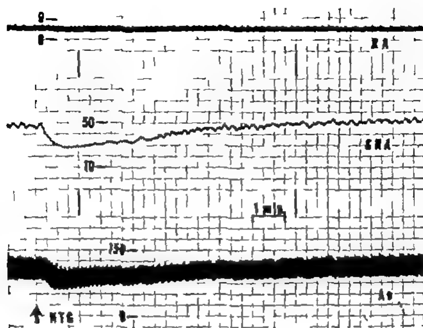


Fig 5 Simultaneous recording of central aortic and retrograde sinus node arterial pressures after intravenous injection of nitroglycerin, 0.1 mg per kilogram.

pressure and pulse were recorded for comparison to that in the sinus node artery of other dogs In these 2 dogs the sinus node was supplied from the left circumflex artery as it is in about 10 per cent of dogs.

Intravenous injections of norepinephrine and epinephrine (0 01 mg per kilogram) and vasopressin (0 1 unit per kilogram) were made in order to observe the effect of elevated central aortic pressure. Similar injections of isoproterenol (1 0 μg per kilogram) and nitroglycerin (0 1 mg per kilogram) were made in order to lower central aortic pressure.

Right atrial contractions were stopped by stimulating the right vagus at the level of the suprasternal notch with an electronic square-wave stimulator at 30 c.p.s. with a stimulus duration of 1 msec for a train of stimuli lasting 6 seconds. Ventricular contractions were stopped alone by initially injecting atropine sulfate into the sinus node artery (10.0 μg in 2.0 ml in 2 minutes) a dose which blocks the response of the sinus node to vagal stimulation for 1 hour Transient atrial fibrillation was produced by faradic stimulation of the right atrial appendage

Results

Retrograde pressure in the sinus node artery ranged from 20 to 60 mm Hg (mean) with an average of 28 mm Hg There was a small smooth-contoured pulse which immediately followed the simultaneously recorded right atrial A wave (Figs. 2 and 3) The pulse amplitude ranged from 2 to 10 mm Hg with an average of 4 mm Hg There was no consistent relationship between control levels of retrograde pressure or pulse and either the size of the dog or the control level of central aortic pressure.

Spontaneous variations in central aortic pressure were accompanied by parallel variations in retrograde pressure in the sinus node artery Injections of pressor agents similarly raised both pressures in a nearly parallel fashion (Fig 4) Agents which lowered aortic pressure simultaneously lowered the pressure in the sinus node artery (Fig 5) During vagal stimulation pressure in the right atrium rose whereas that in the aorta and sinus node artery fell (Fig 6)

Onset of the retrograde pulse was directly after the onset of the A wave in the right atrium and the P wave of the electrocardio-

gram. Since the pulse in the sinus node artery was so far removed from the aortic pulse, the possibility was considered of its being due to the previous aortic pulse with delay due to transmission through arterial anastomoses. However during vagal stimulation escape atrial contractions were regularly associated with a pulse in the sinus node artery whereas escape ventricular contractions (with no P wave) produced no effect in the sinus node artery (Fig 7)

Although norepinephrine raised central aortic pressure and isoproterenol usually lowered it both had a positive inotropic effect on the atrial myocardium and increased the amplitude of atrial contraction. Increased amplitude of atrial contractions was associated with an increased amplitude of retrograde pulse in the sinus node artery regardless of whether the mean retrograde pressure went up or down.

During vagal stimulation contractions of both the atria and ventricles normally ceased and there was no pulse in the sinus node artery (Fig 6) With a preceding injection of atropine directly into the sinus node artery atrial contractions proceeded despite vagal stimulation but there was complete atrioventricular block and no ventricular contractions. During such stimulation after atropine the pulse in the sinus node artery continued in direct relationship to atrial contractions (Fig 8)

Transient atrial fibrillation from faradic stimulation caused the pulse in the sinus node artery to disappear at the same time that organized atrial contractions ceased. While there was irregular atrial pulsation however there was a similar irregular and very feeble pulsation in the sinus node artery (Figs. 9 and 10) With the resumption of normal atrial contraction at the termination of atrial fibrillation there was a prompt return of pulsation in the sinus node artery In contrast to the falling pressure in the sinus node artery with normal pulses during vagal stimulation after intranodal injection of atropine the pressure during absence of pulses because of atrial fibrillation remained normal Thus in these experiments the average retrograde pressure in the sinus node artery was unrelated to the pulsation in the artery

Because of the small size of the sinus node artery (less than 1 0 mm external diameter) we have been unable to measure antegrade pressure in it. The pressure and pulse in the right coronary artery directly at the ostium of the sinus node branch are very similar to the pressure and pulse in the central aorta and change parallel to them.

Retrograde pressure in ventricular arteries has been found by Gregg[4] to be of a low order initially but to increase gradually and on re-examination weeks or months later was found to be nearly the same as normal antegrade coronary arterial pressure presumably because of enlarging

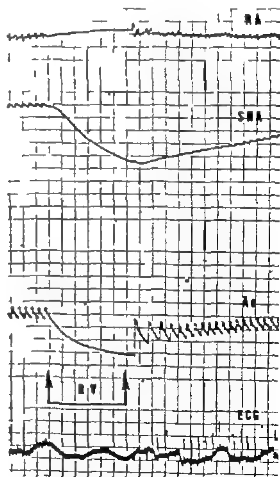


Fig 6 During right vagal stimulation the pressure in the sinus node artery falls while that within the right atrium rises. During cardiac standstill the pressure in the sinus node artery parallels that in the central aorta. Both sinus node arterial and central aortic pressures returned to normal within 30 seconds. This graph illustrates the course of acute events during cardiac standstill. The pressures (*not scaled*) were normal.

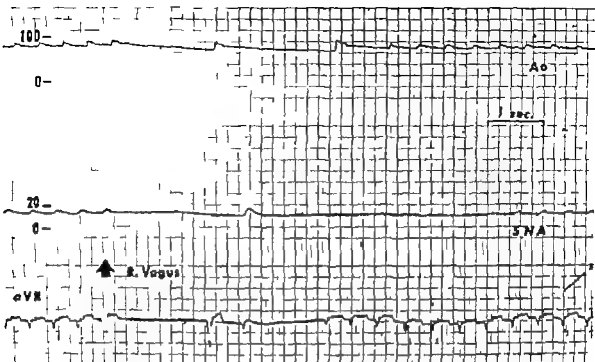


Fig. 7. During vagal stimulation a ventricular escape beat produces a pulse in the aorta but not in the sinus node artery, whereas an isolated atrial escape beat (not conducted to the ventricles) produces a pulse in the sinus node artery only. Mean pressure in the sinus node artery of this dog was originally 28 mm. Hg but gradually became lower as central aortic pressure decreased.

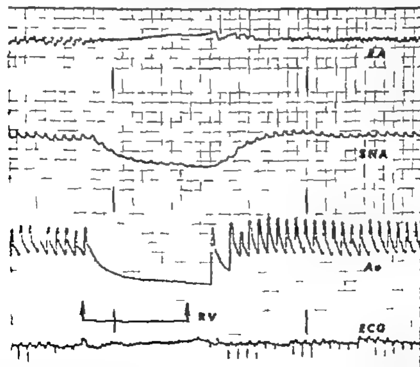


Fig. 8. After selective electroplating of the sinus node through its own artery, vagal stimulation stopped ventricular contractions by blocking atrioventricular conduction. Regular P waves without QRS complexes were recorded in the electrocardiogram. While retrograde pulse in the sinus node artery continued, the retrograde pressure fell just as that in the central aorta did. Paper speed is 10 mm. per second.

routes of collateral arterial circulation. In our studies retrograde pressure in right ventricular arteries was quite low with an average of 2 to 12 mm Hg and was never comparable in magnitude to the pressure in the sinus node artery (Fig 11) Onset of the retrograde pulse in right ventricular arteries just preceded the central aortic pulse but was otherwise very similar to it. Gregg has demonstrated that this earlier rise in retrograde ventricular arterial pulse is due to isometric ventricular contraction.[8] When recorded simultaneously with retrograde pulsation in the sinus node artery that in a right ventricular artery is clearly shown to be dissociated from it (Fig 11) Retrograde pressures in branches of the left coronary artery were much higher than those in branches of the right coronary artery and were usually in the range of pressures observed in the sinus node artery sometimes being higher and at other times lower The contour of the retrograde pulse in ventricular branches of

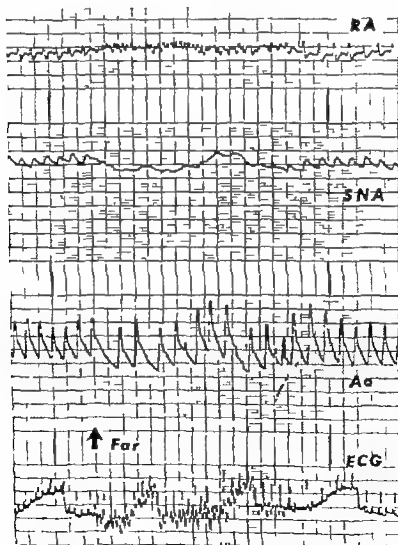


Fig 9 During atrial fibrillation induced by faradization of the right atrial appendage, organized pulsation in the sinus node artery and right atrium disappears, but the pressure in the sinus node artery does not fall. With the resumption of regular atrial contractions the pulse in the sinus node artery returns. Compare to Fig 8.

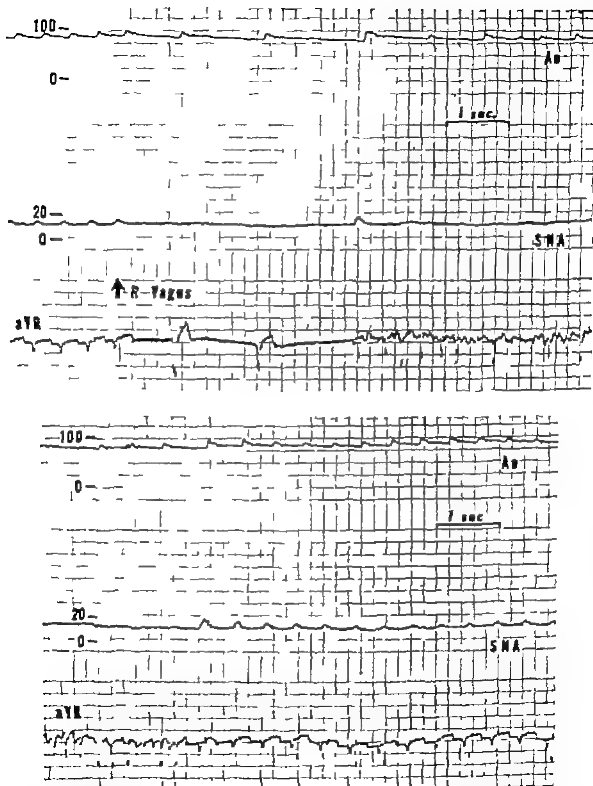


Fig. 10. In this dog vagal stimulation was followed by two ventricular escape beats with associated aortic but not sinus node arterial pulses, then a single conducted sinus escape beat with both pulses, immediately followed by atrial fibrillation. The upper section shows the onset of atrial fibrillation and the lower section shows its termination. With the first sinus beat after fibrillation there is a resumption of regular pulsation in the sinus node artery. A previous experiment in this dog is shown in Fig. 7.

the left coronary artery was similar to that in ventricular branches of the right coronary artery

Retrograde pressure and pulse in right atrial arteries near the sinus node but not perfusing it were much lower than in sinus node arteries in 2 dogs the former was about one fourth the latter Pressure in these non-nodal right atrial arteries was comparable in magnitude to that in ligated right ventricular arteries.

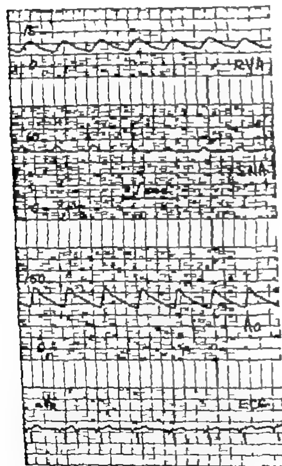


Fig. 11 Simultaneous recording of retrograde right ventricular arterial (*RVA*) and sinus node arterial (*SNA*) pulses. Note that the magnitude of pressure in the ligated right ventricular artery is only a fraction of that in the sinus node artery Retrograde pulsation in ligated ventricular arteries of both the left and right ventricles begins with isometric ventricular contraction and precedes the onset of the central aortic pulse Its complete dissociation from the retrograde pulse in the sinus node artery is demonstrated.

Discussion

Retrograde pressure in the ligated sinus node artery of the dog depends primarily on central aortic pressure Since this pressure cannot reach the sinus node artery in the normal fashion because of a ligature proximal to the origin of the sinus node artery from the right coronary artery it presumably arrives there through arterial anastomoses. This experimental preparation thus lends itself to a study of factors which may affect transanastomotic pressure in the coronary arterial system of the living dog Furthermore the behavior of coronary artery anastomoses may thus be studied without disturbing the circulation to the left ventricle and therefore preserving the principal determinant of both central aortic and coronary arterial pressure.

The relatively high retrograde pressure in the sinus node artery helps to explain why the sinus node continues to function normally after ligation of its primary supply of blood and is consistent with the extensive collateral arterial circulation to the dog's sinus node demonstrable by anatomic studies. This rich anastomosis may be peculiar to the specific area of the node for the retrograde pressure in adjacent atrial arteries of comparable size which did not perfuse the node was much lower

Retrograde pulsation in the sinus node artery depends primarily on atrial contraction although other factors, such as tone of the coronary artery and of arterial anastomoses, quite likely affect it to some degree. Since this pulse is not synchronous with the retrograde pulse in ligated ventricular arteries, it may influence the route or volume of flow in coronary arteries distal to a point of occlusion in a fashion different from the influence of the retrograde ventricular arterial pulse

At present, we have not attempted to measure retrograde flow in the sinus node artery Whether either the retrograde pulse or pressure is a major factor in retrograde flow will await such determinations.

Summary

Retrograde pressure and pulse were studied in the ligated sinus node artery of 37 dogs. The principal determinant of

retrograde pressure is central aortic pressure and the principal determinant of retrograde pulse is right atrial contraction

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Alterations in peripheral blood flow consequent to maximal exercise

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Evaluations of changes in the patterns of local blood flow in the extremities consequent to exercise have been made by several investigators. Grant[1] reported that a sustained contraction of the muscles of the forearm compressed the vessels in that forearm with the degree of compression being dependent on the strength of the contraction. Barcroft and Millen[2] measured the flow of blood through the calf during sustained contractions at various loads and found that the plantar flexors of the foot were almost or quite ischemic during a strong or near maximal contraction. Barcroft and Dornhorst[3] investigated the flow through the calf during rhythmic exercise and reported that pressing a moderately weighted pedal once per second over a short period of time reduced the blood flow by 40 per cent of its normal value.

Other investigators have attempted to determine the recovery blood flow patterns after different exercise stresses. Elsner and Carlson studied the responses of blood flow in the calves of trained and untrained subjects after a brief treadmill exercise at 4 m.p.h. on a 10 per cent grade for 5 minutes. They reported that the group which had undergone training experienced a more rapid recovery of blood flow after the exercise stress, possibly indicating a decrease in the local concentration of vasodilator metabolites during recovery as a result of the training program. McArdle and Verel investigating the responses of blood flow in the forearms of their subjects to different amounts of ischemic work performed at different loads indicated that blood flow responses after ischemia were linearly related not only to the duration of ischemia but to the amount of work performed, except when ischemia or work was of small magnitudes.

Few investigators have attempted to measure the effects of maximal exercise on the recovery patterns of blood flow in the human extremities. The present study was designed to determine the postexercise recovery patterns of blood flow consequent to maximal exercise under conditions of either unrestricted or arrested circulation to the lower limbs during the exercise period.

Method

The subjects were 8 male volunteers, 18 to 30 years of age, who exhibited no physical abnormalities (Table I). Seven experiments were performed on each subject. The first three consisted of riding a bicycle ergometer to fatigue, as evidenced

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by the subject's inability to continue the exercise pace. The next three consisted of the same exercise but in addition the circulation to the lower limbs was arrested during the period of exercise. The final test, for control purposes, was conducted with the subject in the supine position with the circulation to the lower limbs arrested for an interval of 2 minutes, the average duration of circulatory arrest during and after the ischemic exercise in order to evaluate the extent of the hyperemic response to occlusion alone.

Blood flows were measured by the venous occlusion plethysmographic method utilizing the segmental plethysmograph as described by Hyman and Winsor.[6] A venous occlusion pressure of 60 mm. Hg applied directly above the knee and an arterial occlusion pressure of 210 mm. Hg applied at the ankle were used. All determinations were taken with the subject in the supine position. After the subject had rested for 30 minutes in the recumbent position, a series of 16 consecutive determinations of blood flow was made. The average of these was taken as the individual's resting blood flow for that particular experiment. The reproducibility of the methods employed was determined from the results of a preliminary study in which 34 consecutive determinations on the forearm were taken from each of 4 subjects. The standard error of the mean ranged from 1.68 ± 0.03 to 2.55 ± 0.08 ml. per 100 ml. of forearm tissue per minute (Table II).

After the resting determinations were made, the subject mounted the bicycle ergometer. A 3-minute warm up period at 600 Kg.M. per minute preceded each subject's ride to exhaustion at 1,500 Kg.M. per minute, with both work loads being performed at 50 revolutions per minute. After completion of the exercise the subject immediately dismounted and returned to the recumbent position. Postexercise blood flows were then measured for 2 minutes at 15-second intervals starting 1 minute after exercise. In a like manner flows were recorded consecutively for 2-minute intervals every 4 minutes, i.e., 1 to 3 minutes, 5 to 7 minutes, 9 to 11 minutes, etc., up to and including 41 to 43 minutes postexercise.

In the three tests in which circulation to the lower limbs was occluded during the exhaustive effort, a pressure of 300 mm. Hg was introduced into the two thigh cuffs, which were placed as high on the thighs as possible, at that instant at which the work load was increased from 600 to 1,500 Kg.M. per minute. No peripheral pulsations could be detected in these extremities after the application of this pressure.

Electrocardiograms were recorded before exercise, at 1 minute intervals during exercise and the first 10 minutes of recovery, and then at 4-minute intervals until the end of the testing period. The temperature of the skin of the calf and the temperature of the room, as measured by copper constantan thermocouples, were obtained before exercise and at 4-minute intervals after exercise. Throughout the entire study, the temperature of the room varied from 20 to 26°C., with the individual variation for any one experiment never exceeding ± 1 C.

Results

The mean riding time of the 6 subjects with unrestricted circulation during the exercising period was 215 seconds, compared to a mean time of 55 seconds when circulation to the lower limbs was occluded during the exercise.

The temperature of the skin of one calf varied only ± 1°C. during any one test. However, the temperature of the skin of the calf undergoing measurement of blood flow was always 0.2 to 1.8°C. lower than that of the other calf.

At no time were abnormalities noted in the resting or exercising electrocardiograms of the 6 subjects. Only slight differences in the means for the maximum heart rates during exercise were observed between the two exercise conditions. The rates were 180 beats per minute during exercise with unrestricted circulation, and 172 beats per minute with occluded circulation. No correlation was found when the maximum heart rates were compared with the corresponding riding times. Although the resting and maximum heart rates before and during the two conditions of exercise were only slightly different, a significant difference at the 1 per cent level ($t = 11.197$) was noted between the individual recovery

Table I Physical characteristics of the subjects

Subject	Age (yr.)	Height (cm.)	Weight (Kg.)	Surface area (M²)	Volume of calf (ml.)
1	30	183	86	2 08	1 700
2.	25	176	71	1 88	1 300
3	18	188	75	2 02	960
4.	21	183	80	2 02	1 520
5.	26	180	73	1 92	540
6.	27	191	88	2 18	1 160

Table II Variability of blood flow during a single test period

Subject*	Limb volume (ml.)	Number of determinations	Blood flow (ml./100 ml./min.)		Standard error of the mean
			Range	Mean	
Forearm					
1	540	35	1 0–2 1	1 7	0 03
3	500	34	2 1–4 3	2 6	0 08
7	240	34	1 9–3 3	2 6	0 07
8.	200	34	1 0–2 4	1 8	0 06
Calf					
1	1 700	16	0 7–1 0	0 8	0 01
2.	1 300	16	1 2–2 0	1 7	0 06
3	960	16	1 1–1 8	1 3	0 04
4	1 520	16	0 4–0 8	0 6	0 03
5.	540	16	1 3–2 3	1 8	0 06
6.	1 160	16	0 9–1 3	1 1	0 03

*Subjects in the supine position.

Table III Equations of mean flow values

	Primary phase	Secondary phase
All subjects		
Occluded circulation	1 y = −0 40x + 8 67	1 y = −0 06x + 4 06
Unrestricted circulation	1 y = −0 32x + 8 52	1 y = −0 06x + 4 06
Subject 1		
Occluded circulation	1 y = −0 57 + 10 25	1 y = −0 04 + 3 12
Unrestricted circulation	1 y = −0 40x + 8 70	1 y = −0 14 + 5 52

rates. The recovery from exercise with occluded circulation was much faster than from the exercise with unrestricted circulation. By the end of the testing period the mean heart rate under the occluded conditions was near its mean pre-exercise resting level differing by only 9 beats per minute. At the same time the mean rate under unrestricted conditions was still 20 beats above its resting level (Fig. 1).

A high degree of variability among individual subjects' day-to-day resting levels

by the subject's inability to continue the exercise pace. The next three consisted of the same exercise but in addition the circulation to the lower limbs was arrested during the period of exercise. The final test for control purposes was conducted with the subject in the supine position with the circulation to the lower limbs arrested for an interval of 2 minutes, the average duration of circulatory arrest during and after the ischemic exercise, in order to evaluate the extent of the hyperemic response to occlusion alone.

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of blood flow was noted. Subject 3 showed the highest variability ranging from 0.9 to 2.7 ml. per 100 ml. of calf tissue per minute. Subject 1 showed the least variability ranging from 0.8 to 1.2 ml. per 100 ml. of calf tissue per minute (Table II). Peak blood flows after exercise were generally observed within the first 3 minutes of recovery. In the majority of experiments the flows had returned to their resting levels at the conclusion of the test.

The mean recovery blood flow values, under both conditions of exercise were plotted semilogarithmically. Two distinctly separate phases of each recovery curve were observed. The initial phase was characterized by a rapid rate of descent whereas the secondary phase showed a much more gradual slope (Fig. 2). Similar patterns were seen for each individual subject (Fig. 3). Each phase of the recovery curve represented an independent, linear relationship, indicating that both phases of each curve were exponential in nature. An analysis of each phase was made to determine their respective equations. The equations of the mean flow values for all subjects and for an individual (Subject 1) are shown in Table III.

No significant difference was found between the blood flow recovery curves after the two separate exercise conditions. Both curves tended to parallel each other throughout the recovery period.

Patterns of blood flow during the control experiments were quite unlike those found during recovery after either of the two exercising conditions (Fig. 4). Peak flows were obtained within 15 seconds after the restoration of the occluded circulation. The flows then dropped to the resting level within 1 minute and continued to decrease reaching a mean minimum value of 0.5 ml. below the resting level 10 minutes later. At 23 minutes postocclusion the flows had leveled off to values within ± 0.2 ml. of the resting values (Table IV).

The subjects showed little reaction to the control experiments in which circulation to both legs had been occluded for a

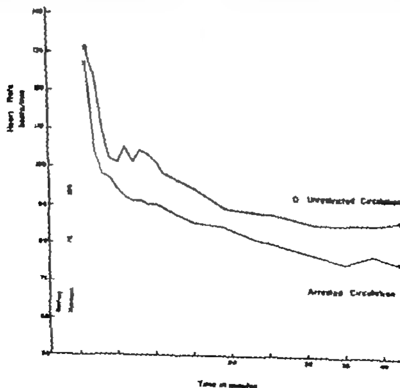


Fig. 5. The recovery pattern of the heart rate after exhaustive exercise with and without circulation to the exercising limbs. The ...

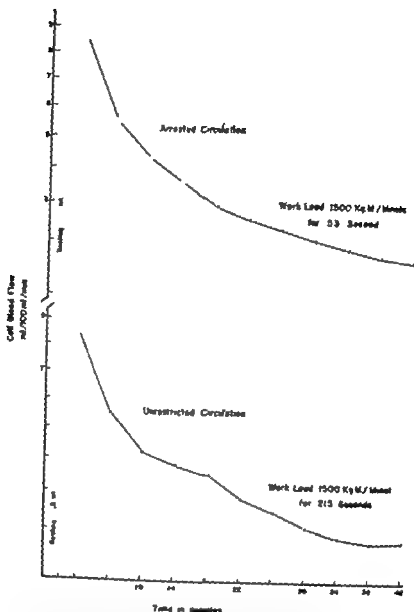


Fig. 2. The recovery patterns of calf blood flow after exhausting exercise with and without circulation to the exercising limbs. The plotted points represent the mean values of each 2-minute interval for the 6 subjects.

brief 2 minute interval. More positive responses were noted both during and after the ischemic exercises. Ten to 15 seconds before the end of exercise the subjects expressed a feeling of general and complete muscular fatigue in both legs. Considerable difficulty in moving from the bicycle to the supine position was observed after the exercise. Shortly after the subject assumed the supine position dull pain was noted in the back and lower legs. When the occluding pressures were released the pain disappeared and apnea which lasted for several seconds occurred and was followed by slow deep breathing and a feeling of warmth in the legs.

Discussion

The subjects' reactions to circulatory occlusion both during and after exercise and during the 2 minute control tests, are relatively consistent with the findings of others.[7]

During the control experiments, there

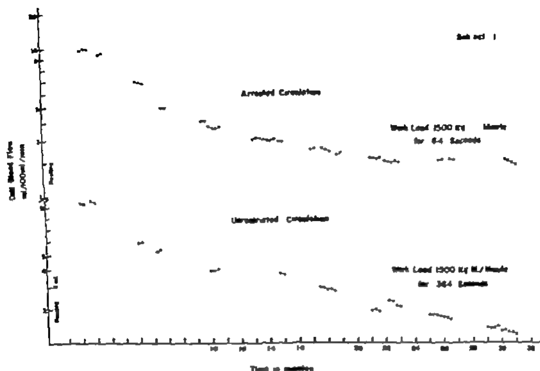


Fig. 3. The calf blood flow of Subject 1 after maximal exercise to fatigue with unrestricted and arrested circulation to the lower limbs during work. The plotted points represent the mean values of three experiments with and three without circulation.

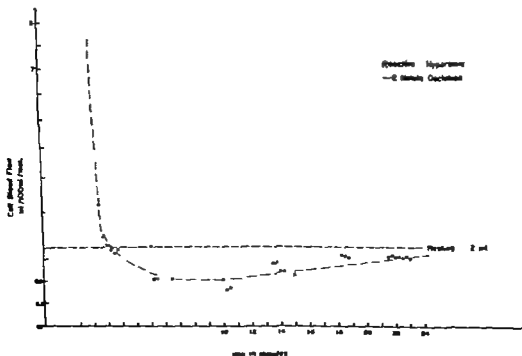


Fig. 4. Reactive hyperemia after 2 minutes of arterial occlusion of the lower limbs. The plotted points represent the mean blood flow values for the 6 subjects.

was a short 1 minute interval during which the blood flow values dropped below their resting levels. Apparently the blood and oxygen debt incurred during the interval of anoxia had more than been repaid during the interval of reactive hyperemia. This finding is in general agreement with the results of other investigators, although the duration of the subnormal blood flow was somewhat greater in the present study.

The recovery blood flow curves after the two different conditions of exercise were similar despite the reduction of the mean work capacity with occluded circulation to one third to one sixth of that with unrestricted circulation. Under the work loads of these experiments, the muscles of the legs were in a state of near maximal contraction during the major portion of the total exercise. Consequently the muscles during contraction were possibly restricting the blood flow to and from the legs in much the same manner that the occlusion cuffs were restricting the flow during the ischemic exercise.[2,8] Since the blood flow responses after both exercise conditions were similar, this suggests that the muscles were working under equivalent degrees of ischemia during the latter stages of both exercises. The time differential between the two conditions of exercise needed to reach this same degree of ischemia existed primarily because in one instance (in which the exercise was performed with occluded circulation) the muscles were working completely under anaerobic conditions, whereas in the other the muscles were working under both aerobic and anaerobic conditions due to the constricting action of the contracting muscles during a near maximal rhythmic exercise.

It would appear that the fatigue experienced under both conditions of exercise was an ischemic or biochemical fatigue in the local tissues which occurred when the supply of available metabolites had been exhausted. Merton has suggested that ischemic fatigue is biochemical in nature and is explained by the fact that because the muscles lack oxygen the biochemical changes underlying the contractile process of the muscles become defective. McArdle and Verel[4] analyzing the factor(s) responsible for the subject's ability to sustain a maximal exercise to fatigue under anaerobic conditions indicated that the role of myoglobin in supplying oxygen and the quantity of oxygen available in the volume of blood trapped in the exercising extremities, was small. They suggested that the biochemical processes concerned with the release and utilization of the energy stored in glycogen and phosphate compounds such as creatine phosphate were the primary factors of importance.

The occurrence of two distinct phases of each recovery curve which has not been reported in previous investigations, may be due in part to the magnitude of the activity. Consequently it is suggested that the appearance of these two phases is related to or was a result of the ischemic working conditions induced by the exhaustive exercise. Since the reactive hyperemic response with its increased blood flow which was observed during the resting experiments could not account for the marked increase in blood flow after exercise with occluded circulation some other explanation must be sought. It is suggested that the initial or primary phase of the recovery curve was in part a function of the reactive hyperemic response caused by the ischemic conditions of exercise and in part as was the secondary phase a function of the normal blood flow debt incurred consequent to exercise.

Similar curves exhibiting the same two-phase characteristics have been noted by other investigators in respect to the recovery oxygen debt after a maximal exercise.[8,1] The first phase of this curve has generally been referred to as the alactacid portion of the oxygen debt and the second phase as the lactacid portion. It is quite possible that a direct relationship exists between the recovery blood flow response and the oxygen debt after a maximal exercise. Elsner and Carlson reported that in their study of postexercise hyperemia in trained and untrained subjects the time for recovery of blood flow was prolonged beyond the time for repayment of the oxygen debt. They also found that training reduced the recovery blood flow whereas the oxygen debt was unaffected which suggests that the two phenomena were unrelated. However the exercise

used in their study was not maximal so that consequently their results and suggestions cannot be specifically applied to the present study.[4]

No direct correlation was found between the mean heart rate recovery and the mean blood flow recovery responses. During the first few minutes of recovery the heart rate decreased at a much faster rate than did the blood flow. At the completion of each experiment, however, the blood flow was approximately back to its pre-exercise resting level, whereas the heart rate was 9 to 20 beats per minute above its pre-exercise level.

The maximum heart rates incurred during exercise were basically the same for both exercise conditions, despite the large difference in total work performed. This can be partially explained by the fact that similar degrees of ischemia occurred during the latter stages of each exercise condition, indicating that the numbers of trapped metabolites present in the working muscles were also similar. The accumulation of these trapped metabolites excited a reflex from the working muscles, resulting in an increased heart rate in both cases. This is in agreement with the conclusions of other investigators who have shown that the heart rate is controlled by impulses arising from the working muscles.[14, 4]

The significant difference between the mean heart rate recovery curves after the two exercise conditions could possibly be explained on the basis of the amount of actual work performed. Brouha reported that the speed of heart rate recovery after exercise depended on the total amount of work performed. He found that the more work an individual performed the slower was his heart rate recovery. However, this may only partially explain these results, since the differences noted between the two curves in the present study were not so great as one might expect when one considers the respective differences in the total work completed.

Summary

Recovery patterns of blood flow were studied after an exhaustive maximal exercise on a bicycle ergometer at 1,500 Kg M per minute under conditions of (a) unrestricted circulation and (b) occluded circulation of the lower limbs. In addition electrocardiograms were recorded before during and after exercise.

Exercising with the circulation to the lower limbs occluded reduced the mean work capacity of each of the 6 subjects to one third to one sixth of his work capacity with unrestricted circulation. The mean maximum heart rates under both conditions were similar. The recovery of the heart rate after the exercise of shorter duration when the circulation had been occluded was much faster than after the longer exercise with unrestricted circulation.

The mean blood flow recovery curves after both conditions of exercise indicated that (a) there was no statistical difference between the mean recovery rates after the two conditions, despite the time differential needed to reach the same level of fatigue and (b) the recovery curves after both exercises were characterized by two distinctly different rates of recovery which followed independent, exponentially linear equations. Although blood flow in the calf had returned to approximately its pre-exercise resting level by the completion of each experiment, the heart rates were still elevated 9 to 20 beats per minute above their pre-exercise level.

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Electrogenesis of the morphologies of the ventricular extrasystolic complexes. I Activation of the interventricular septum

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Daily clinical records often set forth the problem of whether a given ventricular morphology corresponds to a bundle-branch block or is produced by an ectopic ventricular beat. This problem becomes all the more difficult to solve in cases of arrhythmia of the type of ventricular paroxysmal tachycardia or supraventricular tachycardia complicated by bundle-branch block (BBB).[1-3]

Such a difficulty lies in the fact that the mechanism of activation of the heart is somewhat similar in both processes, i.e., its main characteristic is a longer activation time of the interventricular septum.

This problem has become a complex one in recent years, since it has been shown that the duration of the QRS complex cannot be taken as a basis for distinguishing ventricular ectopic morphologies from other morphologies of supraventricular origin.

Recent studies have disclosed that ventricular extrasystoles with normal QRS may be seen in the presence of BBB when the ventricular ectopic beats originate between the P wave and the QRS complex.

The foregoing considerations have led the authors to carry out an experimental work on the mechanism of activation of the interventricular septum of the dog's heart by ectopic impulses at different levels of the free ventricular walls. Experiments were performed under normal conditions as well as under conditions of block produced by a localized lesion of one of the branches of the bundle of His. The influence of ectopic impulses upon the unipolar epicardial records and standard leads has also been investigated.

Material and methods

Twenty-nine dogs which weighed between 6 and 12 kilograms each were used. The preparation employed has been described in detail in previous works.[4-11] The dogs were anesthetized with pentobarbital (35 mg. per kilogram intraperitoneally).

Artificial respiration was applied by means of an intratracheal cannula. The thorax was opened by a mid-sternal incision. The heart was exposed after incision of the pericardium. The arterial pressure

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was recorded throughout the experiment, and the temperature maintained at about 37°C

The leads employed were Lead II for control purposes unipolar leads for obtaining the shapes of complexes at different levels of the heart and bipolar leads for studying the moment of activation and the sequence of the process of activation at the different sites explored The recording apparatus used was a six-channel Schwarzer electroencephalograph Model 504-E. The recording paper ran at a rate of 60 mm. per second Electrical stimuli were rectangular pulses of variable duration and voltage originating in a Grass stimulator Model S4 E

Test stimuli were applied to the free wall of the right ventricle in 16 dogs. In the other 13 dogs, impulses were originated in the free left ventricular wall The mechanism of septal activation was studied under control conditions as well as during the ventricular ectopic impulses In 10 of 16 experiments in which ectopic impulses were originated in the free wall of the right ventricle there was blocking of the right branch In the other 6 blocking occurred in the left branch Of 13 experiments in which stimuli were applied to the free wall of the left ventricle blocking was produced in the right branch in 6 and in the left branch in

Results

The results obtained can be summarized a follow

I Septal activation by two different processes one originating from A V activity as under normal conditions and the other originating in the stimulated ventricular wall In the experiment in Fig 1 the first two complexes in each column correspond to control condition and it may be observed that the bipolar right septal derivation *AA* (*upper tracing*) and left septal record *BB* (*second tracing*) are registered simultaneously unipolar left septal record *B* (*third tracing*) and unipolar left subendocardial *C* (*fourth tracing*) present morphologies of the QS type Unipolar left subepicardial record *D* (*lower tracing*) shows morphologies of the RS type Under these control conditions the R-R interval between the two bipolar right septal record *AA* or between the two bipolar left septal records *BB* is 341.3 msec.

The third complex in column I corresponds to a propagated response to stimuli applied to *S* It may be appreciated that the interval between the bipolar right septal record *AA* of the extrasystole and the immediately preceding control record is reduced to 333 6 msec. whereas the interval between the bipolar left septal records *BB'* remains 341.3 msec. In other words, the bipolar right septal record *AA* is obtained 5 msec earlier than the bipolar left septal record *BB'* Under these conditions the unipolar left septal record *B* (*third tracing*) and the unipolar left subendocardial record *C* (*fourth tracing*) assume morphologies of the rS type whereas the unipolar subepicardial record *D* (*lower tracing*) remains RS in type with an increase in the positive component lessening of the negative component and increased QRS

The third complex in columns II III and IV corresponds to propagated responses to stimuli applied to S_1 It may be seen that the interval between the bipolar right septal record *AA* of the extrasystolic complex and the immediately preceding control record is reduced to figures of 330 321 6 and 316.6 msec respectively whereas the interval between bipolar left septal records *BB* remains 341.3 msec In other words, the bipolar right septal record *AA* of the ectopic response in column II is registered 11 3 msec. earlier than the control record whereas bipolar left septal record *BB* is still recorded under control conditions. In columns III and IV the bipolar right septal records *AA* of the extrasystole are registered 19 7 and 25 msec. earlier than the control records respectively whereas the bipolar left septal record *BB* is still registered as under normal conditions.

Unipolar left septal record *B* unipolar subendocardial left record *C* and unipolar subepicardial left record *D* show a progressive increase in the positive component decrease in the negative component and increase in the duration of QRS

Fig. 2 corresponds to the same experiment previously described and shows the relation between the activation times at the sites already described It can be observed that with impulses which origi

nate in the right free ventricular wall (S_1) the right endocardial septal bipolar *AA* shows activation earlier than the left *BB'* this left septal bipolar *BB* shows activation as under normal conditions (supraventricular impulses) The activation time relations between the left septal bipolar *BB* the left subendocardial *CC'* of the free ventricular wall and the subepicardial *DD* remain the same as under control conditions.

II Relation between the activation of free ventricular walls and interventricular septum by impulses originating in the free right ventricular wall Fig 3 corresponds to an experiment in which four separate sites of the heart were explored with neighboring bipolar leads *AA* located on the right septal endocardial surface at the level of the anterior papillary muscle *BB'* at the same level on the subepicardial surface of the free right ventricular wall in the mid zone of the lateral aspect *CC'* on the endocardial left septal surface in the mid zone of the middle third and *DD'* in the subepicardial zone on the lateral surface of the free left ventricular wall Test stimuli were applied to *S* at the same level as the trabecular zone in the free wall of the right ventricle.

Column I presents the control conditions It may be observed that the QRS has a duration of 31 2 msec in L_{II} (*lower tracing*) whereas the P R interval is 82.5 msec The bipolar left septal endocardial record *CC'* (*third tracing*) is recorded 5 6 msec. earlier than the bipolar right septal endocardial record *AA* (*upper tracing*) Activation in the bipolar right subepicardial record *BB'* (*second tracing*) occurs 1.8 msec. later than that in the bipolar right septal endocardial record *AA* The bipolar left subepicardial record *DD'* (*fourth tracing*) is recorded 15 msec. later than the bipolar left septal record *CC'* The time of registration of the bipolar left septal record *CC'* is demarcated in Lead II by a dotted line whereas the activation time of the bipolar right septal record *AA* is shown by a solid line

In column II stimulation was made at *S* and early activation of the right bipolar epicardial *BB'* was obtained 1 2 msec. earlier than that of the right septal bipolar *AA* It can be observed that the P R interval is shortened to 80 msec and that the duration of QRS is likewise shortened to 26.2 msec., with an increase in the Q wave Under these conditions the bipolar left septal record *CC'* (*third tracing*) is recorded 2.5 msec before the bipolar right septal record *AA* (*upper tracing*) The bipolar left subepicardial record *DD* (*fourth tracing*) is registered 15 msec. later than bipolar left septal record *CC'*

The relationship between the activation times of both septal surfaces and the free ventricular walls is conclusive, in the sense that the interventricular septum is activated by two different processes one originating from the stimulation of the free right ventricular wall the other corresponding to the normal activation process. Consequently septal activation is accomplished by two wave fronts—that originating from the supraventricular impulse and that originating from stimulation of the free ventricular wall.

Column III corresponds to another propagated response which originates from the right ventricle, with the following characteristics the duration of QRS in L_{II} (*lower tracing*) is 29 3 msec. with a P R interval of 76.8 msec The bipolar right septal record *AA* is registered 3 7 msec before the bipolar left septal record *CC'* This indicates that the septal activation process at this level has been reversed and now takes place from right to left. The bipolar right subepicardial record *BB* is recorded 2.5 msec before the bipolar right septal record *AA* As will be seen from the following columns, the duration of QRS increases as the P R interval becomes shorter whereas the bipolar left septal record *CC'* is activated later than the right septal record *AA* In this experiment the greatest difference in activation time between bipolar septal records *AA* and *CC'* was 20 6 msec

III With left BBB the impulses originating in the free right ventricular wall do not modify the QRS complex in L_{II} the activation time relations of the explored left and right septal surfaces were not altered In the experiment corresponding to Fig 4, two separate sites of the interventricular septum were explored with neighboring bipolar leads *AA* situated on the mid zone of the middle third of the left septal endocardial surface and *BB'* on the right septal endocardial surface immediately above the anterior papillary muscle. Test stimuli were

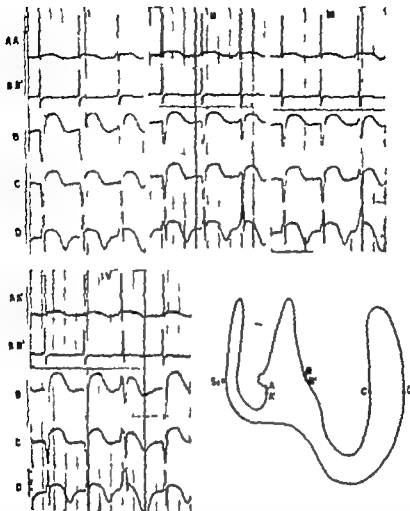


Fig. 1. Two different sites on the ventricular septum explored by means of neighboring bipolar derivations: AA' on the right septal endocardial surface under the anterior papillary muscle and BB' on the left septal endocardial surface at both the junction of the middle and lower third and in the middle zone of the septum at the same level as bipolar derivation AA'. Two points on the free left ventricular wall were also explored with unipolar lead C on the subendocardial surface of the free wall in the middle zone of the lateral aspect and D on the subepicardial surface at the same lead point as unipolar subendocardial lead C. All columns show bipolar right septal record AA' (upper tracing) and bipolar left septal record BB' (second tracing) obtained simultaneously with unipolar left septal record B (third tracing), left subendocardial record C (fourth tracing), and left subepicardial record D (lower tracing). Test stimuli were applied to S on the lateral aspect of the free right ventricular wall.

applied to S_1 on the lateral aspect of the free wall of the right ventricle.

Column I shows control L_{II} (*upper tracing*) recorded simultaneously with unipolar left septal lead A (*second tracing*), bipolar left septal record AA' (*third tracing*) and bipolar right septal record BB' (*lower tracing*). L_{II} shows morphologies of the R type and a duration of the P-R segment of 83.3 msec. Unipolar left septal record A (*second tracing*) is of the QS type; the bipolar left record AA' (*third tracing*) is recorded 11.6 msec. before the bipolar right septal record BB' (*lower tracing*). In other words, left septal zones explored by AA' are activated before right septal zones explored by BB'.

Column II shows the same leads as those described above after the production of

left BBB Under these conditions it may be observed that L_{II} remains predominantly positive with an increase in the duration and voltage of QRS The P R segment increases slightly to 93.3 msec. which is due to the fact that the ventricular activation now starts in the right septal endocardium. The unipolar left septal record *A* (*second tracing*) assumes morphologies of the rS type, whereas registration of the bipolar left septal record *AA* (*third tracing*) occurs 30 msec. later with respect to the bipolar right septal record *BB'* (*lower tracing*) This indicates that the general septal activation process has been reversed having a predominance from right to left.

Column III shows the same leads as those described above with complete left BBB and stimuli applied to *S* and continuously recorded. The frequency of test stimuli was slightly greater than the sinus frequency and the interval between two test stimuli was 8.3 msec shorter than the interval between two sinus discharges. As a result, the stimuli gave rise to a propagated response which started between the P wave and the

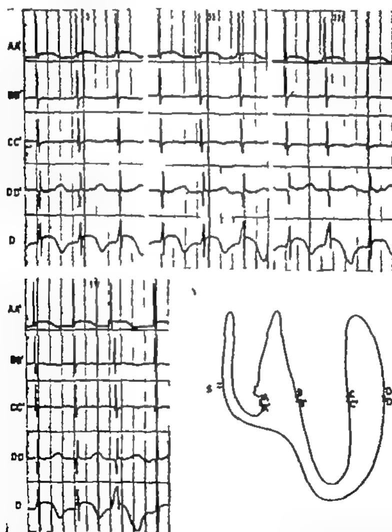


Fig 2 Same experiment as that depicted in Fig. 1 showing the relation between the activation times of the four sites explored. With impulses which originate in *S* the right septal endocardial bipolar *AA* activates before the left one, *BB'* Bipolar tracings *BB'* *CC'* and *DD'* maintain the same relationship which they had under control conditions.

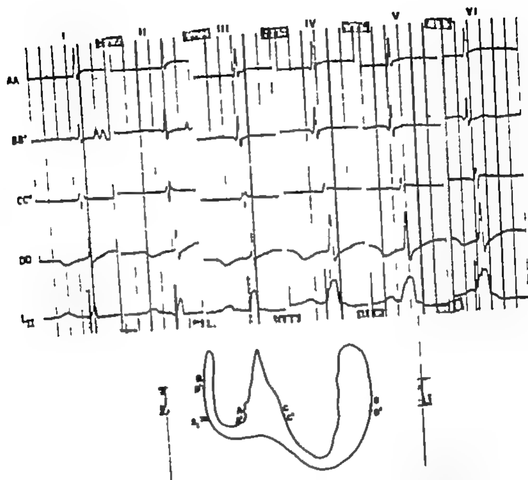


Fig 3 Four sites of the heart explored by neighboring proximal bipolar derivations *AA* and *BB* on the right pert and *CC'* and *DD'* on the left. Test stimuli were applied t *S* t the same les 1 the free right entric lar wall t different times in the cardiac cy le. Different follow-beat morphologies were obtained Activation of the four proximal bipolars and their relation- h p t morphologies obtained L_{II} are investigated

QRS complex This caused an earlier occurrence of the ventricular activation process which manifested itself by a shortening of the P R interval The first two complexes of column III show the same characteristics as described in column II The third complex shows a shortening of the P R interval which becomes 83.3 msec. L_{II} still presents the same characteristics as in control column II The unipolar left septal record *A* (*second tracing*) remains rS in type with a slight increase in the positive component. The bipolar right septal record *BB'* (*lower tracing*) i registered 30 msec before the bipolar left septal record *AA* (*third tracing*) In the following complexes the P R interval progressively shorten until it d s-

QRS Under these conditions the morphology obtained in L_{II} as well as in the unipolar left septal record *A* shows no changes at all as compared with the control in column II The bipolar left septal record *AA* (*third tracing*) is registered 30 msec. after the bipolar right septal record *BB* (*lower tracing*)

II With right BBB impulses originated in the free right ventricular wall modify their QRS complexes in L_{II} and the activation time relations of septal segments is altered In the experiment corresponding to Fig 5 two separate sites were explored by mean of bipolar leads obtained from the interventricular septum *AA* located on the left septal endocardial surface at the junction of the middle and lower thirds, and *BB* on the right septal endocardial surface

ord *AA*. Test stimuli were applied to S_1 in the trabecular zone of the right ventricle.

The control conditions can be appreciated in column I. L_{II} (*upper tracing*) presents predominantly positive morphologies with a P-R segment of 78.3 msec. The unipolar right septal record *B* (*second tracing*) is of the rS type, whereas the bipolar left septal record *AA* (*third tracing*) is obtained 16.6 msec. before the bipolar right septal record *BB* (*lower tracing*).

The data in column II were obtained after complete right BBB. It may be seen that L_{II} (*upper tracing*) assumes morphologies of the RS type with slurrings and notchings in S and a longer duration of QRS than that obtained in the control record.

The P-R segment remains 78.3 msec. The unipolar left septal record *A* (*second tracing*) is of the QS type. Activation of the bipolar left septal record *AA* (*third tracing*) occurs 26.6 msec. earlier than that of the bipolar right septal record *BB* (*lower tracing*). This is good evidence of the significance of the degree of block thus obtained.

Column III shows the leads described above, with complete right BBB and stimuli applied to *S* on the free right ventricular wall. The first complex presents the same characteristics as those mentioned in column II. In the second complex, L_{II} (*upper tracing*) assumes morphologies of the RS type with a marked decrease in the duration of QRS, whereas the P-R segment is shortened to values of 75 msec. The unipolar left septal record *A* (*second tracing*) remains QS in type, with an important decrease in the duration of QRS as compared to the control record in the first complex. The bipolar right septal record *BB* (*lower tracing*) is recorded 21.[illegible] msec. later with respect to the bipolar left septal record *AA* (*third tracing*). Both the shortening of the

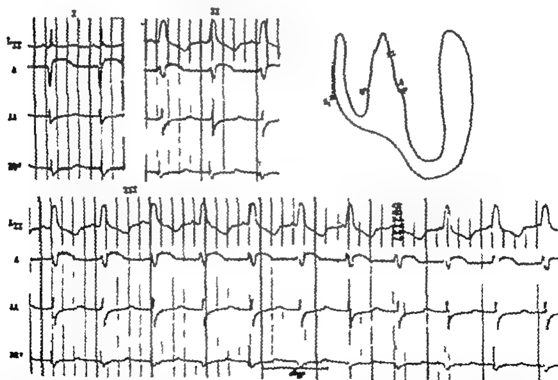


Fig. 4. T[illegible] ties removed from the interventricular septum. *AA'* on the left septal endocardial surface in the middle zone of the middle third and *BB'* on the right septal endocardial surface above the anterior papillary muscle. Test column I shows L_{II} (*upper tracing*) obtained simultaneously with unipolar left septal record *A* (*second tracing*) and bipolar *AA'* (*third tracing*) and *BB'* (*lower tracing*). Column II shows the same derivations as column I after complete left BBB. Column III presents the same conditions as column II plus impulses originated at the same level in the right ventricle (*S*) at different times in the cardiac cycle.

P R segment and the decrease in activation time of the bipolar right septal record *BB* as compared to that of the bipolar left septal record *AA* are indicative of a response of the right ventricle to stimuli applied to *S*.

The third complex corresponds to another response of the right ventricle to stimuli at *S*. Under these conditions it may be observed that the P R segment is shortened even more to values of 68.3 msec. L_{II} assumes morphologies which are very similar to those of the control records in column I whereas the unipolar left septal record *A* remains QS in type with a shorter QRS. The bipolar left septal record *AA* is registered 15 msec earlier than the bipolar right septal record *BB*.

In the fourth complex the P R segment is reduced to figures of 66.6 msec. L_{II} assumes predominantly positive morphologies of the R type with slurrings in the ascending limb of R and a longer duration of QRS which becomes more evident in successive complexes. The unipolar left septal record *A* becomes rS in type, and registration of the bipolar left septal record *AA* occurs 1.6 msec later than that of the bipolar right septal record *BB*. This indicates that the general process of septal activation has been reversed and takes place from right to left. In the following complexes, one may appreciate that the P R segment is shortened more and more whereas the bipolar left septal record *AA* is registered later than the bipolar right septal record *BB*. In the last complex the bipolar left septal record *AA* is registered 26.6 msec later than the bipolar right septal record *BB*. A figure closely resembling that obtained with left BBB is obtained in L_{II}.

Column IV presents the same data as column III developed in an inverse manner. The P R segment is seen to increase in a progressive manner until it reaches its normal values in the last two complexes.

Discussion

Like other investigators who have previously dealt with this problem[13,15] our experiments have shown that impulses which arise in the free ventricular walls are propagated in the interventricular septum from the stimulated side toward the opposite side. Thus, the process of septal activation takes longer. Such a delay which occurs whenever the activation is due to ventricular ectopic impulses is caused by an early activation of the septal muscular mass of the stimulated side as compared with the general process of ventricular activation.

When the wave of septal activation which arises from ventricular ectopic impulses is produced at an early moment in the cardiac cycle, i.e. when the interval between the normal and the extrasystolic complex is very short, the general process of septal activation is the longest, with a predominance in the sequence of activation of the septum from the side on which the impulse is originated to the opposite side. On the other hand, when a ventricular ectopic impulse is produced at a given moment in the cardiac cycle near the normal complex, the interventricular septum is activated by two wave fronts from opposite directions. One of these arises from the ventricular ectopic impulse and invades the septum on the endocardial surface corresponding to the stimulated side toward the thickness of the septal muscular mass; the other arises from the supraventricular impulse and descends through the corresponding limb to the non-stimulated side, extending from the endocardial surface into the septal mass. This gives rise to a considerable decrease in septal activation time. It also confirms the findings of others that the delay in the septal activation process is related to the moment of the cardiac cycle at which the ectopic impulse is produced.

When the ventricular ectopic impulse originates immediately after the functional refractory period of the tissue, the longest septal activation time is obtained. Whenever a section of the branches of the bundle of His is produced, several points should be taken into account.

Ectopic impulses which are produced in the ventricle opposite to the blocked side normally give rise to a sequence of septal activation from the side in which the impulse is originated to the contralateral side, that is to say, it follows the same direction as the bundle branch block. Under these condition the delay of the process of septal activation is always the same in each extrasystole, identical with the delay obtained in bundle-branch block.

Stimuli applied to the blocked ventricle give rise to impulse causing an earlier occurrence of the activation process of the septal mass from the stimulated side. The delay which the process of activation undergoes in the blocked ventricle[11,12] is compensated for by an earlier occurrence of activation time on account of ventricular ectopic impulses. When such a delay is identical with the earlier occurrence produced in the activation of the blocked ventricle by an ectopic beat a complex will result which has the same characteristics as the normal complex. This is due to the fact that two wave fronts are produced in the interventricular septum which are activated from both surfaces to the center of the septum. Predominance of the wave front occurs from left to right, giving an average direction of septal activation from left to right, as described by Lewis,[17] Scher[14] Medrano[3-22] and Sodi Pallares[20] and associates, for the greater part of the interventricular septum. Under these conditions the shortening of the P R segment indicates an earlier occurrence of ventricular activation caused by the extrasystole.

Stimuli applied to the blocked ventricle at very early stages of the cardiac cycle give rise to impulses which occur earlier in the septal activation process on the blocked side (the side on which the stimulus is applied). This originates a predominance of the wave front of septal activation from the ectopic impulse over the opposite wave front of supraventricular origin. Under these conditions the general sequence of the septal activation process is effected in a direction opposite to that of the sequence followed during bundle branch block. The difference in activation time between the two septal surfaces is identical with that obtained with bundle-branch block.

When ventricular ectopic impulses are originated immediately after the P wave the resulting morphologies are very similar

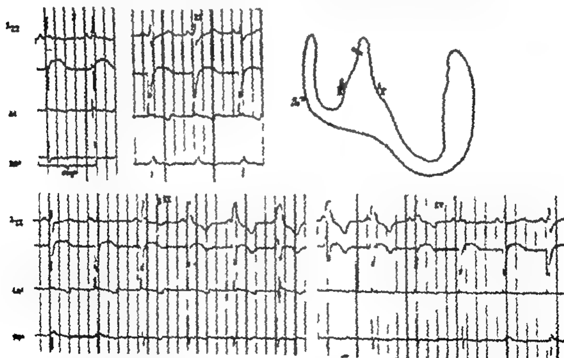


Fig. 5. T... sites on the interventricular septum explored by proximate bipolar derivations AA' on the left septal endocardial surface and BB' on the right septal endocardial surface at the same lead point as AA'. Control column I shows L_2 (upper tracing) simultaneous with unipolar right septal endocardial record B (second tracing) and bipolars AA' (third tracing) and BB' (lower tracing). Column II shows L_{II} (upper tracing) with complete right BBB obtained simultaneously with unipolar left septal endocardial record A (second tracing) and bipolars AA' (third tracing) and BB' (lower tracing). Columns III and IV show the same conditions as column II plus impulses originated at the same level as the free right ventricular wall (S) at different times in the cardiac cycle closely resembling the accordion effect.

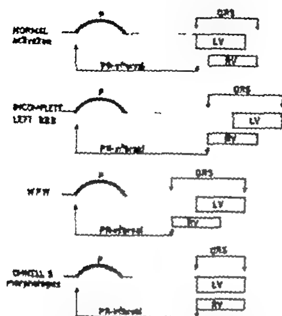


Fig. 6. Shows in schematic form the activation of the heart during normal conditions, with incomplete left BBB in the WPW syndrome type B and in Öhnell's [illegible]

to those observed in the Wolff-Parkinson-White (WPW) syndrome as suggested by several authors. In our experiments no WPW morphologies have been found in the epicardial records from either the septal or anteroseptal zones of the heart. The WPW morphologies were always obtained in the anterolateral and lateral sides of the left ventricle. Accordingly, if such morphologies are ascribed to a fusion beat mechanism [illegible] the latter will be found to be in accordance with the WPW type B. As a matter of fact, it has not been possible to reproduce the WPW type A by stimulation of the free wall of the right ventricle.

A vectorcardiographic analysis performed by Wolff[24] has disclosed the fact that the delta wave coincides with the first vectorcardiographic loop. On the basis of this finding, Wolff suggests that such a wave originates in the interventricular septum. The same phenomenon was investigated by Bleifer and associates, who maintain that the delta vector replaces the septal vector in the WPW syndrome. Our experiments likewise indicate that the initial slurring of QRS in morphologies of the WPW type takes place simultaneously with an early activation of the right septal mass.

An analysis of the various morphologies of the WPW type as performed by us has disclosed a number of morphologies which have the same varieties as those described by Öhnell[17] and Fox.[25]

Our findings have shown this to occur whenever activation of the interventricular septum starts almost simultaneously from the endocardial surfaces toward the inside of the septum. In this case the duration of QRS is shortened due to a diminution in the activation time of the septum. Under these conditions, other morphologies may be obtained which have an initial negative deflection (Q wave) at the same level as the free wall of the left ventricle as well as at L_{II}. This deflection originates in the vectorial resultants of the free right ventricular wall and has a general sequence of activation from endocardium to epicardium as demonstrated by other investigators.[12] Tranchesi and associates,[26] in their study of WPW morphologies, suggest that the Q wave of the left precordial leads is due to variations in the SA delta. Our experiments have shown that these waves are due to the activation of the free wall of the right ventricle. Such an activation takes place in an early stage in relation to the septal activation process.

Information presented herewith can be summarized in the diagram shown in Fig. 6, which depicts in schematic form the different activation patterns depending on the relation between activation of both ventricular masses. (a) In normal condition the left ventricle is activated before the right. (b) In incomplete left BBB the late activation of left septal zones explains the disappearance of Q waves and the early slurring of the ascending limb of R. (c) In WPW syndrome type B the early activation of right septal zones determines the shortening of P-R and QRS morphologies similar to those observed in incomplete left BBB. (d) In Öhnell's variants the simultaneous activation of left and right zones reduces the total activation time and consequently the duration of QRS.

Summary

A study has been made of the form of activation of the interventricular septum by ectopic impulses produced in the free ventricular walls. It has been demonstrated that under these conditions the time of sep[illegible]

tal activation is longer than normal because there is an earlier occurrence of the activation of the septal surface on the stimulated side as compared to the activation of the contralateral septal surface (due to supraventricular impulses). According to our experiments, the septal activation is subjected to a double command: one from the ectopic ventricular focus, and the other from the supraventricular impulse through the opposite branch as far as the stimulated ventricle. Two waves of activation originate in the interventricular septum in opposite directions. The wave front coming from the ectopic impulse will be the greater the earlier the septal activation according to the moment of the cardiac cycle at which the impulse is produced.

It has been shown that the morphologies of the unipolar epicardial records depend on the degree of delay which the process of activation undergoes in the interventricular septum.

In bundle branch block, ventricular morphologies may be obtained which are identical with the normal control morphologies whenever ectopic impulses are produced on the blocked side. This is due to the fact that the ectopic ventricular impulse anticipates the process of septal activation previously delayed by bundle branch block. The extrasystolic complex is recognized under these conditions by a shortening of the P-R segment.

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A technique for postmortem coronary arteriography

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The use of diagnostic coronary arteriography has re-emphasized the anatomy of the coronary circulation to the clinician, the surgeon, and the radiologist. The pathologist has long been aware of the complexities of this circulation. In fact, previously described methods for the supplementary postmortem demonstration of the coronary circulation were usually developed by pathologists themselves, since dissection of the coronary vasculature is technically difficult and often incomplete. Unfortunately, because previously advocated methods for injection of solidifying or contrast materials into coronary vessels were difficult to perform and very time consuming, they were not widely adopted.

It is the purpose of this paper to describe a simple and rapid method of postmortem coronary arteriography. This technique can be used easily by the pathologist, radiologist, or clinician to study coronary artery disease roentgenographically.

Materials and method

The equipment used for this technique is shown in Fig. 1. No special apparatus is needed. The cannulas are No. 15 blunt needles with rubber or plastic connectors. The contrast medium utilized is Lipiodol.

The best results are obtained by using a heart freshly removed from the pericardial sac. However, the technique has been utilized with success in hearts refrigerated 6 to 12 hours. The disadvantage in this situation is that the tissues are friable and the coronary vessels may be ruptured at the time of insertion of the cannulas. Blood and postmortem clots are removed from the heart chambers by immersion in running tap water. It is not necessary to flush out the coronary arteries themselves and postmortem clotting is not a problem.

The aorta is transected immediately above the aortic valve, which facilitates the cannulation of the coronary ostia. The main pulmonary artery is transected and careful blunt dissection of the surrounding connective tissue separates it from the base of the aorta. This exposes the most proximal portion of the left coronary artery. The proximal 1 to 2 cm. of each coronary artery is dissected free of surrounding connective tissue. It is not necessary to strip the vessel of all the surrounding tissue, but enough must be removed so that the cannulas can be tied securely in place.

Care must be used in exposing the origin of the left coronary artery because of its early bifurcation into the left anterior descending and left circumflex branches. Also, the preventricular branches of the right coronary artery may originate in the most proximal portion of the parent vessel.

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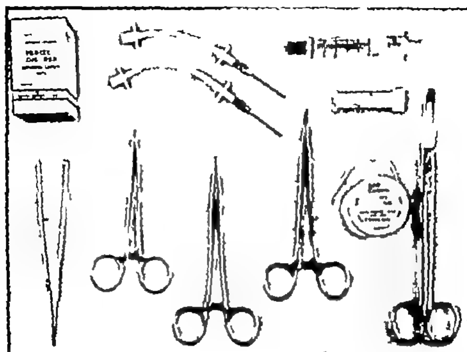


Fig. 1. Injection equipment. Lipiodol, two No. 15 blunt cannulas, 5-c.c. syringe, silver surgical clips, No. 2-0 cotton suture, scissors, hemostats, and blunt forceps.

These usually are covered by fat tissue on the surface of the heart and can be easily overlooked.

This simple blunt dissection of the proximal arteries from the surrounding tissue is all that is required to prepare for cannulation. A metal surgical clip is then attached within the base of the aorta at each coronary ostium. These will facilitate the measurement of the distance between the ostium and plaques and obstruction observed on the roentgenograms.

Various types and sizes of cannulas have been used to inject coronary arteries. The blunt No. 15 metal cannulas with approximately 3 inches of rubber or plastic tubing and connectors are adequate. A smaller size may be desirable if there is narrowing of the proximal vessel with extensive arteriosclerotic plaques. A flanged tip catheter will be easier to tie in place but may be difficult to insert into a diseased vessel. Usually 2 or 3 ligatures of No. 2-0 cotton sutures will secure each cannula after it has been passed through the coronary ostium into the lumen of the artery.

After the two cannulas have been tied in place (Fig. 2) an anteroposterior roentgenogram of the specimen is obtained. A cardboard cassette at table top will give excellent detail. Generally, 60 to 70 kilovolts with 100 milliamperes and $\frac{3}{4}$ second at 36 inches will result in roentgenograms of good quality.

The coronary arteries are then injected with Lipiodol. It is preferable to inject the right coronary artery first. Steady firm pressure is applied to the 5-c.c. syringe containing the iodized oil and connected to the tubing of the cannula. The oil should flow with ease into the vessel. Filling is usually complete when resistance prevents further injection at this steady pressure. This usually requires 3 to 5 c.c. of oil for the right coronary artery. If there is increased resistance early in the injection there may be an obstruction of the lumen of the vessel in its proximal portion. Excessive pressure can rupture the vessel or distort the morphologic findings. Therefore a film should be obtained in order to evaluate the cause of resistance before the injection is continued. Fig. 3 demonstrates the method of injection.

Anteroposterior and lateral roentgenograms are then obtained. For the lateral projection an additional 10 kilovolts usually give adequate penetration.

If filling is incomplete and there is no evidence of obstruction more oil is injected and the film is repeated. The distribution of the right coronary artery is variable but usually the contrast media will fill the marginal artery to the apex of the heart and the right circumflex artery to the region of the interventricular septum. When this occurs, the left coronary artery is injected.

It is frequently necessary to inject separately the anterior descending branch and the left circumflex branch of the left coronary artery because of their early bifurcation. If the cannula can be tied securely in the main artery, however, it will be possible to fill both branches with a single injection. The hand injection is again done with the same steady pressure described above.

Four to six cubic centimeters of oil are usually required to fill the branches of the left coronary artery. Again, when resistance is felt the injection is stopped and anteroposterior and lateral films are obtained. Serial films may be needed to follow roentgenographically the injection to completeness. Occasionally oblique or stereoscopic projections will be helpful in demonstrating areas of abnormality in the vessels.

The average time consumed in the preparation of the specimen, injection of the arteries, the roentgenographic exposure, and processing of the films is approximately 1 hour. After interpretation of the films the specimen is returned intact to the pathologist for dissection.

Results

Two illustrative cases are presented.

Case 1. This 62-year-old white man was hospitalized because of a 24-hour history of substernal pain with extension to the left arm. The electrocardiogram was interpreted as showing diaphragmatic myocardial infarction. He died 36 hours later.

Autopsy disclosed a hemopericardium. A fresh hematoma was present on the posterior wall of the heart. The coronarogram (Fig. 4) demonstrated incomplete filling of the left ventricular branch of the right circumflex artery and extensive irregularity of the lumens of the main coronary vessels.

Dissection of the specimen revealed the complete obstruction of the left ventricular branch of the right circumflex coronary artery by a recent thrombus, a recent posterior septal myocardial infarction with rupture of the posterior left ventricle, and severe generalized arteriosclerosis.

Case 2. This 54-year-old white male physician with a history of mild angina pectoris developed chest pain 3 days prior to admission to the hospital. This pain was progressive and not relieved by nitroglycerin and narcotics. He was admitted in shock and died 1 hour later. Serial electrocardiograms over the preceding 11 years had been normal, except for one obtained 3 weeks before death which showed minimal S-T segment depression.

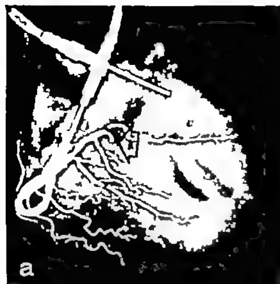
The postmortem coronarogram (Fig. 5) demonstrated marked arteriosclerotic changes in the anterior descending branches of the left coronary artery and the right coronary artery. There was

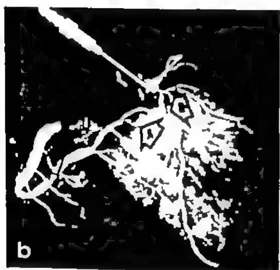


Fig. 2. Preparation of specimen. The proximal portion of each coronary artery has been exposed. The blunt cannulas have been inserted through the coronary ostia and are secured in place with ligatures around the vessels.



Fig. 3. Injection of left coronary artery. Simple hand injection of the iodized oil is performed using steady firm pressure. The right coronary artery is usually injected first.





complet obstruction of the left circumflex rtery The utopsy revealed complete occlusion of the circumflex branch of the left coronary artery by recent thrombus nd severe arteriosclerotic coronary rtery disease

Discussion

The injection of an opaque material intravascularly followed by roentgenographic visualization has been used extensively in the study of the circulation in general. As early as 1896 solidifying contrast media were used to inject blood vessels in postmortem specimens. Since that time many opaque injection materials have been utilized at autopsy in an attempt to obtain a detailed study of the anatomy and pathologic condition of the circulatory system. Mercury and mercury salts red lead lead chromate colloidal silver sodium bromide salts of barium bismuth and calcium and iodized oils are but a few of the contrast materials that have been used

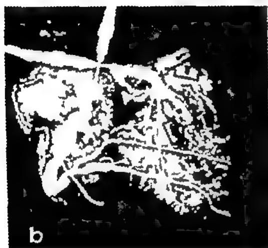
It is not surprising that the interest of early investigators became centered upon the study of the vascular network of the heart. In fact it was through the use of more detailed methods of examining the heart at autopsy that the complex relationship between coronary occlusion and myocardial infarction became apparent.

The best known method for the postmortem roentgenographic examination of the coronary circulation is that of Schlesinger[1] He injected over 1,500 specimens



Fig 4 Case 1 I jection of the right coronary artery demonstrated incomplet filling of the left entricular branch of the right circumflex artery (A). b nd a Anteroposterior nd lateral projections. The left coronary artery has been injected There is extensiv irregularity nd narrowing of the lumen of the anterior descending branch due t arteriosclerotic plaques (B). The right coronary rtery is also involved, especially in it proximal portion evidenced by the linear lucencies of extensiv plaques (C). The obstructed branch of the right coronary rtery is gain identified (A). The metallic X marker is t the si f the gross infarct on the posterior wall of the specimen Not ill approximation t the obstructed essel.





with a lead agar mass which required detailed preparation and great care in handling. The method was technically difficult and cumbersome. More recently Schlesinger and his associates[2] advocated the use of a new solidifying mass composed of gelatin, potassium iodide, formalin and barium sulfate. This material could be used at room temperature so that it was no longer necessary to submerse the specimen in warm saline. However, a complex injection apparatus using compressed air and pressure controls was necessary. Also, there was delay in examination of the specimen because of the time necessary for solidification of the mass. Schlesinger also developed an "unrolling" technique of dissection of the heart. Its purpose was to spread the vascular networks into a single plane in order to facilitate their identification on the roentgenograms. This added to the complexity of his method and altered the specimen for subsequent examination.

The method described in this paper is not subject to these objections. The practice of leaving the organ intact prevents any distortion of the circulatory pathways and preserves the specimen for the pathologist's complete dissection. The Lipiodol requires no preparation and its viscosity makes it an ideal medium. It fills the arterioles with homogeneity but does not flood the capillaries, and does not reach the cardiac chambers. Another important feature is that Lipiodol does not interfere with the gross or microscopic dissection



Fig. 5 Case 2. The plain film demonstrates marked calcification in the walls of the coronary arteries. The metal clips mark the coronary ostia. *b* Both coronary arteries have been injected. There is extensive irregularity and narrowing of the lumen of all the main arterial branches. There is almost complete occlusion of the main anterior descending branch of the left coronary artery (*A*). The left circumflex artery is completely occluded 1.5 cm. from its origin (*B*). *c* The lateral view again demonstrates the marked arteriosclerotic changes in the anterior descending branches of the left coronary artery (*A*) and the right coronary artery (*C*). The obstruction of the left circumflex is also seen (*B*).

In addition, Lipiodol affords excellent roentgenographic detail. The routine anteroposterior and lateral views of the unopened organ adequately demonstrate the morphology.

The technique of Schlesinger and variations of his technique used by other investigators have contributed greatly to the knowledge of the basic anatomy and pathology of the coronary vessels. However, the complexity of these techniques has limited their more general utilization. The method described in this paper fulfills the need for a rapid and simple technique for postmortem coronary arteriography.

Summary

A simple method for the postmortem roentgenographic demonstration of the arterial supply of the human heart is described. This technique eliminates the disadvantages of previously utilized methods in that it is technically simple, is less time consuming, and does not alter or destroy the specimen for subsequent gross or microscopic examination. The roentgenograms taken of the heart after injection of the iodized oil into the coronary arteries have vividly demonstrated arteriosclerotic plaques, occluded vessels, and the pathways of collateral circulation. These advantages make this method readily adaptable for routine postmortem examination of the coronary circulation.

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The effect of digoxin in normal man on the cardiorespiratory response to severe effort

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It is now generally agreed that the contractile force of the normal heart of both man and animal is increased by the administration of digitalis.[1-3] There is, however, lack of agreement as to the effect of digitalis in normal man upon the cardiac output at rest and during mild or moderate exercise. For many years it was accepted that digitalis was contraindicated in normal man because of reports that digitalis would significantly decrease the cardiac output in dogs and normal man.[3-] More recent studies have been in disagreement relative to this question. In 1958 Williams reported that digitalis in normal man resulted in a decreased cardiac output during moderate exercise with a slower heart rate so that the stroke volume was but little changed. However, Seltzer, Goodyer, and Rodman have since reported essentially no difference in cardiac output either at rest or after mild exercise in normal human subjects.

We could find essentially no information relative to the effect of digitalis upon normal man during exhausting exercise. From the previously available physiologic information one could reasonably argue either that digitalis would increase or that it would decrease the ability of normal man to carry out severe exercise. Moreover, the effect of digitalis upon the cardiac rate and rhythm during strenuous exercise has not been sufficiently documented. The purpose of the present investigation was to explore these questions utilizing the measurement of oxygen uptake, pulmonary ventilation, and cardiac rate and rhythm during multiple levels of exercise of progressive severity to the maximal effort tolerated by the subject.

Methods

Ten volunteer normal male subjects were studied. Five of these ranged in age from 20 to 29 years and five ranged from 30 to 39 years. Each subject was studied three separate times; these included a control with no capsules, after a placebo capsule containing magnesium oxide and vegetable coloring, and after digoxin capsules. Both types of capsules were prepared in our hospital pharmacy to have a similar appearance. Magnesium oxide in the doses used (0.1 Gm.) has no effect.[11] A digitalizing dose of digoxin, ordinarily 3.0 mg. depending on the size of the subject, was given in 1 day, and the subject was maintained on 0.5 mg. of digoxin daily for 3 days including the day of the procedure.

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The placebo capsules were given on the same schedule. The subjects were started alternately on one of the two types of capsules in the order in which they entered the study.

Each subject was studied on the fourth day after beginning the digitalis or placebo. In general, the procedure of Mitchell and associates[12] for determinations of the maximal oxygen uptake was carried out. The subject was allowed a 10-minute warm-up exercise at a grade of 3 degrees and 3 miles per hour on the motorized treadmill employed.* After a 10-minute rest he was subjected to a series of 2½-minute periods of exercise on the treadmill. Recent studies by Astrand and Saltin[13] indicate that the time required for the attainment of a satisfactory steady state during exercise depends on the severity of exercise. With maximal or near maximal exercise such a condition is reached after 1 minute of exercise. With less severe exercise a period of to 5 minutes might be required. Therefore, the 2½-minute periods of exercise utilized in this study might be too brief for complete achievement of a steady state at the lower levels of exercise but should be entirely adequate at the higher levels. The speed was kept constant at 5 miles per hour, a fast walking speed. The grade was increased stepwise by 1 degree for each period of exercise from an initial grade of 5 or 6 degrees until exhaustion precluded the individual from attempting or completing another more severe exercise.† The subjects were all volunteers from the student body and faculty of the Medical College of Alabama. They were all engaged in cardiorespiratory research and were motivated by an attitude of scientific inquiry and by a sense of competition. A rest of 7 to 15 minutes was allowed between each exercise, the longer period after the more severe effort. Expired gas was collected into a Tissot gasometer over a period of 1 minute from 1½ to 2½ minutes of each period of exercise. The tank was washed out with the gas expired from 40 to 55 seconds of exercise. A two-way Collins plastic "J" valve which had an inspiratory resistance of 0.8 cm. of water at a flow of 100 liters per minute and 2.0 cm. of water at a flow of 200 liters per minute, was utilized. The expiratory resistances of this valve were 1.4 and 4.8 cm. of water at flows of 100 and 200 liters per minute, respectively. Corrugated tubing with an internal diameter of 25 mm. and 70 cm. in length connected the valve to the gasometer. The volumes of expired gas were determined by direct measurement from the spirometer. Samples of this gas were analyzed for oxygen and carbon dioxide content by the micro-Scholander technique.

The heart rate and rhythm were monitored during the exercise by electrocardiographic recordings. The limb leads were fixed high on the chest by a rubber strap and the unipolar exploring lead (V lead) electrode was attached to the forehead by an elastic band.

The technically most satisfactory lead was used (this varied from subject to subject). The electrocardiogram was recorded frequently during the periods of exercise and recovery but especially during the last 12 seconds of exercise and the first 5 seconds of recovery. The rate during the last 10 seconds of exercise was used as the maximal heart rate. Although there were artifacts due to motion on the tracings during the most violent efforts, the records allowed an accurate assay of rate and rhythm.

Results

All 3 days of exercise were considered in the evaluation of the severity of the exercise as compared to the studies of others, but when analysis was made for the effect of digoxin, only the placebo was used for comparison. The mean age of subjects in this study was 29.9 ± 5.3 years, the mean height was 178.4 ± 6.2 cm., and the mean weight was 73.3 ± 11.8 kilograms.

Oxygen intake. The average greatest oxygen uptake in the 20 to 29-year age group was 44.1 and 42.7 milliliters per kilogram per minute (ml./Kg./min.) for the control and placebo studies, respectively. With digoxin this group had 40.6 ml./Kg./min. as the mean highest oxygen uptake. The 30 to 39 year age group had mean greatest oxygen uptakes for control and placebo

*Collins [illegible] Serial [illegible] Warren E. Collins, Inc., Boston, Mass.

†The percentage grade is obtained by multiplying the [illegible] of the angle of inclination of the treadmill by 100.

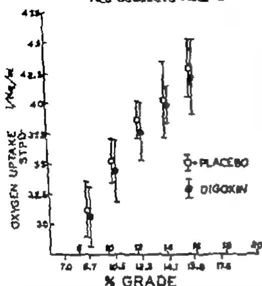


Fig. 1. Average oxygen uptakes, in cubic centimeters per kilogram per minute, with standard deviations for all subjects at different elevations of the treadmill, for the placebo and for digoxin. The uptakes are similar for each level of work.

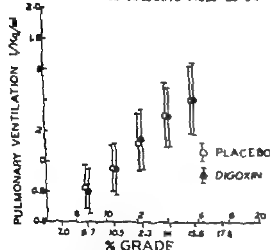


Fig. 2. Average pulmonary ventilation, in liters per kilogram per minute, with standard deviations for all subjects at different elevations of the treadmill, for the placebo and for digoxin. The ventilation is similar for each level of work.

tests of 43.5 and 43.4 ml. Kg. min., respectively. This group had 43.5 ml. Kg. min. as the average peak oxygen uptake after digoxin.

The minute oxygen uptakes were compared for each per cent grade of treadmill elevation for all subjects (Fig. 1). The uptakes were quite similar between the placebo and digoxin conditions at each level of work. There was no significant difference for the highest oxygen uptake calculated as milliliters per kilogram per minute between the placebo and the digoxin when the age groups were considered separately (20-29, $p < .159$; 30-39, $p < .460$) or when the group was considered as a whole ($p < .460$).

Pulmonary ventilation. The average greatest pulmonary ventilations in the 20 to 29-year age group were 1.67 and 1.52 liters per kilogram per minute (BTPS) for the control and placebo studies, respectively, and 1.53 L./Kg. min. after digoxin. The 30 to 39-year age group had greatest mean pulmonary ventilations of 1.40 and 1.42 L./Kg. min. for the control and placebo studies, respectively. With digoxin this group had 1.41 L. Kg. min. as the mean greatest pulmonary ventilation.

Mean pulmonary ventilation compared to per cent grade of treadmill elevation is shown in Fig. 2. The lack of difference for the control and digitalis observations is striking.

There was no significant difference for the highest pulmonary ventilation calcu-

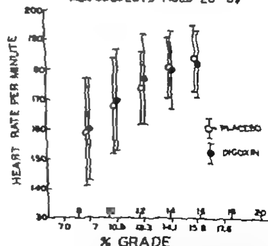


Fig. 3. Average heart rate per minute with standard deviations for all subjects at different elevations of the treadmill, for the placebo and digoxin. The heart rate is similar for each level of work and tends to level off at the two highest elevations.

lated as cubic centimeters per kilogram per minute between the placebo and the digitalis when the groups were considered separately (20-29 $p < .460$ 30-39 $p < .067$) or when the group was considered as a whole ($p < .345$)

Heart rate. For the 20 to 29-year age group the average greatest heart rate was 193 and 185 beats per minute during the control and placebo studies and 186 beats per minute after digoxin. In the 30 to 39-year age group the maximal heart rates achieved were 185, 186, and 182 during the control, placebo, and digoxin experiments, respectively.

There was no trend of difference of average heart rate after the placebo or the digoxin when compared to the per cent grade of treadmill elevation, as seen in Fig. 3. The rates tended to reach a plateau around 180 beats per minute under all three conditions. There was no significant difference between the highest heart rates on placebo or on digoxin when the groups were considered separately (20-29 $p < .382$ 30-39 $p < .345$) or when the group was considered as a whole ($p < .184$)

Changes in rhythm. There were no arrhythmias during the control, placebo, or digoxin observations. Technical qualities of the electrocardiogram at these levels of exercise did not permit detailed analysis, although no gross changes in the S-T segment or T waves were observed. One subject (in age group 30-39) when on digoxin showed a P-R interval which was shorter before than immediately after exercise at two levels of work (0.16 second before and 0.23 second immediately after exercise and 0.18 to 0.20 second before with 0.22 second immediately after exercise) and a P-R interval which was longer before than immediately after exercise at one level of work (0.18 to 0.20 second before exercise and 0.14 second immediately after exercise). There was no correlation with grade of exercise or heart rate with these observations.

The digitalizing dose of digoxin given 3.0 mg. in all but one subject (T. J. R., who took 4.0 mg. because he was a large individual) is an ordinary amount used in the treatment of congestive heart failure. Although it is difficult to say when a normal subject is digitalized,[20] certain subjects had some effects which are usually found after digitalis. Four out of the 10 subjects suspected correctly that they were on digitalis because of epigastric discomfort. Four out of 10 showed a slower resting heart rate of from 3 to 42 a minute,[7] and 1 showed no change in comparison with the placebo. Five showed an increase of from 8 to 27 per minute. All subjects, of course, were mentally prepared for the "all out" muscular exercise. Five of the 10 showed T wave changes at rest after digoxin, and it was difficult to render a decision about S-T segment or T wave changes in the other 5 because of the technical quality of the chest-strap electrocardiograms.

Five subjects showed a P-R interval which was longer by 0.01 to 0.05 second when on digoxin than when on the placebo, averaging 0.036 second longer on digoxin. Three showed no change in the P-R interval, one showed an increase of 0.01 second, and another an increase of 0.03 second on digoxin.

Discussion

The ability of an individual to increase his oxygen uptake during exercise in proportion to the severity of the work may be used as an index to the over-all effectiveness of the circulation in the absence of pulmonary disease.[21,22] The absolute limit of this ability has been utilized for this purpose by many investigators in attempts to determine the so-called maximal oxygen uptake of normal and abnormal subjects.[23,24] It has become apparent that this term is somewhat misleading, since it is very difficult to measure the true maximal oxygen uptake in a reproducible fashion and since it may vary with the muscles used[15] and type of exercise performed. It has become evident, however, that a significant alteration in circulatory function of a given individual will change the oxygen consumption during work at maximal or near maximal levels. In other words, a significant impairment of the circulation would result in a diminished oxygen consumption in proportion to severe work, especially as maximal tolerated levels are reached.[25] Conversely, an improvement in circulatory capacity would have the opposite effect. This is shown by the observation that athletes have a greater

ability to increase the oxygen uptake than do untrained subjects.[31]

In the present study the greatest reliance in interpretation was placed on the relationship of the oxygen uptake to the external work (grade of inclination of the treadmill) at maximal or near maximal effort rather than on the absolute level of the maximal oxygen uptake achieved for the reasons already mentioned. However since the severity of the effort was the maximal that these untrained but well motivated subjects were able to tolerate under the conditions of these experiments it seems likely that the greatest oxygen uptakes were in fact very nearly true "maximal oxygen uptakes" as this term is generally used. This possibility is supported by the maximal heart rates attained by the ventilatory volumes reached during such a short period of exercise and by the absolute levels of oxygen uptake per se. Thus, the average maximal oxygen uptakes achieved during this study (42.5 ± 4.0 ml./Kg. min. and 43.5 ± 2.8 ml./Kg. min. during all experiments for the 20 to 29 and 30 to 39 year old subjects, respectively) compare favorably with the values reported for such subjects by others. Using very similar methods of testing Mitchell, Sproule and Chapman[12] found the mean maximal oxygen uptakes of subjects not actively in training at ages 20 to 29 and 30 to 39 years to be 44.7 ± 3.9 and 39.3 ± 3.3 ml./Kg. min. respectively. Robinson[27] reported mean values of 48.7 and 43.1 ml./Kg./min. for these age groups. The values for pulmonary ventilation during the maximal effort of the subjects of the present experiment (1.573 ± .275 L./Kg. min. for the 20 to 29-year old subjects and 1.471 ± .177 L./Kg. min. for those 30 to 39 years old) likewise are comparable. Robinson[27] reported values of 1.64 L./Kg. min. and 1.55 L./Kg./min. for comparable subjects. The heart rate during maximal aerobic work has been shown by Robinson to be a declining function of age.[27] At ages 8 to 12 years the mean maximal heart rate was found to be 198 beats per minute whereas at age 25 years the maximal rate was 190 beats per minute and 185 beats per minute at age 35. At age 60 years the maximal heart rate was decreased to 165 beats per minute. Similar values have been reported by other investigators.[22] The maximal heart rates attained in the present study are very comparable to these values.

The above observations strongly support the probability that the greatest levels of oxygen uptake achieved by the subjects of the present study during the control and placebo conditions were or were very nearly the maximal possible for the type of exercise employed. It has been shown that the administration of digoxin in ordinary therapeutic doses had no significant effect on this "maximal or near maximal" oxygen uptake, the pulmonary ventilation, or the heart rate or rhythm. From these facts we can conclude that digoxin in such doses does not significantly alter the capacity for aerobic work of the normal individual. This is tantamount to saying that digoxin does not alter the effectiveness of the circulation in normal man. Since the primary function of the circulation is to deliver oxygen to the tissues the measurement of the maximal oxygen uptake is a direct assay of the functional capacity of the circulation. It not only allows one to study quantitatively the effects of disease[1] but also to readily detect differences in the physical fitness of normal man.[31]

The physiologic relationships of the maximal oxygen uptake have recently been investigated by Mitchell, Sproule and Chapman.[12] These investigators made direct observations of cardiac output, oxygen uptake, arteriovenous oxygen difference and the oxygen tension of arterial and venous blood during multiple levels of exercise to and beyond the maximal oxygen uptake. Their conclusions were that (1) cardiac, not pulmonary factors, either ventilatory or diffusive, were the determinants of maximal oxygen uptake, and (2) the cardiac factors were the ability to increase cardiac output and to widen the arteriovenous oxygen difference, the latter primarily by decreasing the mixed venous oxygen content. Their data also showed that maximal cardiac output and maximal oxygen uptake were achieved at the same level of exercise and that when this level was exceeded both variables decreased.

From the foregoing and from the classic Fick equation relating cardiac output and

oxygen consumption, it is evident that the results of the present study relative to the fact that the maximal oxygen uptake was unaltered by digitalis could theoretically mean that cardiac output and arteriovenous oxygen difference were unaltered or that exactly reciprocal variations in cardiac output and arteriovenous oxygen difference occurred. The former possibility seems much the more likely for a number of reasons. As already cited, disease states which restrict cardiac output also restrict the maximal oxygen uptake. Moreover, disease states in which the cardiac output is subnormal are characterized by an increased ventilatory equivalent for oxygen, in contrast to the findings of the present study. The mechanism for this hyperventilation is not known, but appears to be related to the degree to which anerobic metabolism is being utilized. Similar reasoning can be applied to the heart rates, especially at submaximal work levels. In addition, the absolute levels of arteriovenous oxygen difference found by Mitchell and associates[12] for normal subjects at maximal oxygen uptakes were slightly greater than 14 volumes per cent, leaving little room for further expansion. Since nonexercising organs and tissues which extract relatively little oxygen continue to receive blood, even though at reduced rates during exercise. Regardless of these considerations, however, the fact remains that the maximal aerobic capacity of the normal human being is unaltered by digoxin under the conditions of these experiments.

This study is one primarily of exercise and the effect that digoxin may have thereon. As regards cardiac output, information concerning digitalis is consistent in dogs[1-23] and divergent in human beings at rest or during mild exercise. The decrease in cardiac output is secondary to a peripheral effect on venous return in the dog,[4,22] and this may play a role in the human subject.

Of the two physiologic effects of digitalis—the cardiac effect, which tends to increase cardiac output, and the peripheral effect which tends to decrease cardiac output[4]—the peripheral effect seems to predominate in the dog. However, in human beings it is possible that the two effects neutralize each other, since no change has been found in cardiac output at rest and during mild exercise after digitalis.[4-] The present data support the previous findings in the human subject, in that even with the stress of maximal exertion when the cardiovascular system is operating near capacity,[3] there was no change in the maximal oxygen uptake, ventilation, or pulse rate after digoxin. It seems likely that exercise is such an overwhelming stimulus to the cardiovascular system that its effect on the peripheral circulation predominates over whatever restrictive influences might be present as a result of the administration of digoxin.

The conclusions of this study are in agreement with the recent studies of Goodyer[4] and of Rodman[18] and their collaborators relative to the response of cardiac output to mild or moderate exercise in normal subjects after the administration of digitalis. The explanation offered by Rodman and associates for the differences between these studies and those with opposite conclusions by other workers[7] relative to the timing of the exercise in relation to the initial digitalizing dose of the cardiac glycosides seems to be very reasonable. They[1] found an immediate decrease in resting cardiac output after intravenous Cedilanid; however, the cardiac output returned to control levels 2 hours later. Seltzer[8] also found, after an intravenous dose of digoxin, a slight immediate decrease in cardiac output, which was, however, not significantly different from the control observations within 1 hour after the injection.

Except in subjects with auricular fibrillation, it is difficult to determine when there is optimal digitalis effect, both in patients with cardiac decompensation and in normal individuals. Lown and Levine[21] and also Friend indicate the current standard techniques of the oral administration of digoxin, which include the giving of the digitalizing dose averaging between 2.0 and 4.0 mg. over a period that ranges from 6 to 24 hours. The average and most effective maintenance dose without toxicity is 0.5 mg. daily.[21,2] The duration of a digitalizing dose of digoxin is 4 to 7 days, averaging 5 days.[21,2] In this study it is believed that the subjects were digi

talized in the usual sense of the word because of (1) the initial doses of 3.0 mg over a 10-hour period (4.0 mg in one instance), (2) the maintenance dose of 0.5 mg daily including the day of the experiment, (3) the epigastric discomfort in 4 of the 10 subjects, (4) the definite T wave changes in 5 out of the 10 subjects, and (5) the P-R interval which averaged 0.036 second longer on digoxin in 5 of the 10.

The over-all response of normal digitalized man including the heart rate and rhythm to severe stress found in the present study adds further support to the position taken by Goodyer and Rodman that there is probably no physiologic contraindication to the administration of the dosage used in the present study to persons who have no overt evidence of cardiac insufficiency. It has been suggested by Willman and associates[20] that prophylactic digitalization might be of value in the maintenance of cardiac function during and after the various stresses encountered by the myocardium during open-heart surgery. The present studies would tend to support their view that prophylactic digitalization would not alter the transport of oxygen to tissues prior to, during, and after surgery.

Summary

Ten untrained normal males who ranged in age from 20 to 39 years were studied during treadmill exercise at moderate to exhausting levels of work. The maximal oxygen uptake, pulmonary ventilation, and heart rate compared well with peak levels found in the literature for subjects of similar age, habits, and weight. The values of the three variables at each level of work agreed well in each individual on three different occasions. Digoxin in therapeutic doses had no measurable effect on oxygen uptake, pulmonary ventilation, or heart rate at any level of work, including up to and the maximal tolerated by each subject. It was concluded that the maximal aerobic capacity for work of normal man is not altered by therapeutic doses of digoxin.

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The significance of factors modifying the development of isoproterenol induced myocardial necrosis

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In 1958 during the course of some comparative toxicity studies, we observed that a synthetic adrenergic bronchodilator which structurally resembled isoproterenol caused massive myocardial necrosis in the rat. By testing isoproterenol (1 /3 4-dihydroxyphenyl/ 2-isopropylamino ethanol HCl) in multiple dose levels we developed a pharmacologic technique for producing in the rat an infarct-like myocardial necrosis of uniform severity[4] which resembles closely human myocardial infarction. This observation has been confirmed by other groups who used this method for a model in studying the problems of experimental myocardial infarction. -[9]

In subsequent experiments, in order to investigate the pathogenesis of the isoproterenol heart necrosis, we have studied several endogenous and exogenous factors which were thought to have an effect upon the development of this lesion. The results of some of these experiments have already been published. These will be reported only in summary form here and the reader can receive full information in the related papers. The effect of sex hormones and starvation on isoproterenol heart necrosis are original studies and will be described in detail

Endogenous factors and isoproterenol cardiac necrosis

In an experimental series we investigated the role of breed age weight and sex of the animals on the severity of cardiac necrosis elicited by isoproterenol.[10] In four strains of rats we could detect no significant difference in their sensitivity to isoproterenol although Sprague-Dawley rats had somewhat less severe myocardial lesions than did two different inbred colonies of Wistar rats or hooded rats of the Long Evans strain. A direct relationship was found between the weight of the animals and the severity of myocardial necrosis. Young rats with low body weight were less sensitive to the cardiotoxic effect of isoproterenol than were large rats.

Studies investigating the sex dependability of isoproterenol cardiotoxicity showed that male rats were more sensitive than females if a correlation was drawn according to their age. If however male

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and female rats of similar weight were studied, their cardiotoxic response was similar. Thus the apparent greater sensitivity of male rats to isoproterenol was attributed to their faster rate of growth and their larger body weight.

Effect of hormones on isoproterenol heart necrosis

a. Effect of sex hormones. In another experiment in rats of the Long Evans strain the effect of the administration of exogenous sex hormones, such as natural conjugated equine estrogen (Premarin), estrone, progesterone, and testosterone, was investigated on the development of isoproterenol myocardial necrosis. The average weight of the males was 323 ± 9 grams, that of the females was 205 ± 6 grams. For each compound, two groups of rats were used, 10 males and 10 females. Each of the three compounds was administered in doses of 1 mg. per rat per day subcutaneously for 7 days. One milligram of compound was dissolved in 0.2 ml. of sesame oil. Control rats were given 0.2 ml. of sesame oil in the same way in which the hormones were administered. On each of the last 2 days of the experiment, isoproterenol was given in dose of 85 mg. per kilogram subcutaneously. Forty-eight hours after the first injection the rats were killed and autopsies were performed. The hearts were weighed and the heart lesions were graded according to a system described previously.

As can be seen in Table I, Premarin and progesterone did not influence significantly the severity of isoproterenol heart necrosis. The testosterone-treated animals had a higher mortality rate, greater cardiac enlargement, and somewhat higher grades of cardiac necrosis than did the controls. Similar findings were present in the estrone-treated males.

b. Thyroid function. On the basis of the known correlation between thyroid function and epinephrine sensitivity,[13] a study was performed to investigate whether a similar relation might exist between thyroid function and isoproterenol cardiotoxicity. It was found that thyroidectomy and pretreatment with propylthiouracil decreased or abolished prostration and the mortality which follow the administration of isoproterenol. Hypothyroid rats had smaller heart weights and less severe heart lesions at every dose level than did their respective controls. Pretreatment with thyroxin, on the other hand, aggravated the clinical symptoms, increased the mortality rate and heart enlargement, and the severity of the myocardial necrosis was accentuated.

c. Adrenal steroids. The effect of adrenal cortical hormones was investigated on intact as well as on adrenalectomized rats. It was found that, provided adrenalectomized animals were maintained on sodium chloride, their response to the cardiotoxic action of isoproterenol was the same as that observed in intact rats. Whereas ACTH and glucocorticoids failed to influence isoproterenol cardiotoxicity, mineralocorticoids such as DOCA and fluorocortisol markedly aggravated the cardiac necrosis elicited by isoproterenol. The clinical symptoms were severe and prolonged, the mortality rate was high, and the cardiac necrosis was of almost maximal severity.

Effect of salt content of diet on development of isoproterenol heart necrosis

The aggravation of cardiotoxic response to isoproterenol in animals treated with DOCA or fluorocortisol was thought to be a reflection of the action of these steroids on electrolyte metabolism.[4] To prove this hypothesis, we undertook experiments in which the role of dietary electrolytes on isoproterenol cardiac necrosis was studied.[3] The aggravating effect of DOCA on isoproterenol cardiotoxicity was abolished by giving supplementary KCl to rats pretreated with DOCA. The severity of the heart necrosis of these rats was in the same range as that of the rats kept on a normal diet. Rats on a potassium-deficient diet had more severe heart necrosis after isoproterenol than did those on a normal diet. Deficiency of sodium produced an amelioration of the isoproterenol cardiac necrosis at all dose levels. Addition of sodium to a potassium-deficient diet increased the mortality rate and augmented the severity of cardiac necrosis. Thus it became apparent that there is an inverse relationship between the concentration of

Table I. Effect of sex hormones on the isoproterenol cardiac necrosis

Group	Mortality	Relative heart weight	Grade of necrotic heart lesions
Males			
Control	1	428 ± 11	3.4
Premarin	0	427 ± 18	3.6
Estrone	3	478 ± 32	3.8
Progesterone	1	444 ± 12	3.5
Testosterone	3	485 ± 25	4.0
Females			
Control	0	438 ± 22	2.7
Premarin	0	435 ± 11	3.0
Estrone	0	457 ± 17	3.0
Progesterone	0	420 ± 11	3.3
Testosterone	3	460 ± 24	3.5

Each compound was given subcutaneously in doses of mg. per rat per day for 7 days in 0.2 ml. of sesame oil. Controls received the vehicle. Isoproterenol was given subcutaneously in doses of 85 mg. per kilogram on the last 2 days of the experiments.

electrolytes K^+ and Na^+ in the diet and their effect on the isoproterenol cardiotoxicity.

Effect of high-fat and high-carbohydrate diet on isoproterenol cardiotoxicity

The dietary aspect of isoproterenol cardiac necrosis was further investigated by Balazs and associates.[17] These authors observed that a diet high in fat or carbohydrate markedly increased the isoproterenol cardiotoxicity. Rats which received the high-fat or high-carbohydrate diet were of normal body weight for their age but had an increase in the percentage of body fat. It appeared that the toxicity of isoproterenol was not increased until body fat increased above a critical level. Their conclusion was that the increased content of body fat and not the fat content of the diet per se was responsible for the aggravation of isoproterenol cardiotoxicity. Balazs and associates have shown moreover that this aggravation was further accentuated by so-called "isolation stress." This was revealed by the more severe cardiac necrosis in individually caged rats after the administration of low doses of isoproterenol than in the rats kept in colonies.

Effect of starvation on isoproterenol cardiac necrosis

During the investigation of the effect of electrolyte composition of the diet on the isoproterenol cardiotoxicity, we observed that fasting during the night before the administration of isoproterenol markedly reduced the mortality rate and severity of cardiac necrosis in rats kept on a combination of potassium-deficient and sodium-supplemented diet. Since according to our previous experience, this combination was the most effective in aggravating isoproterenol cardiotoxicity, it seemed worth while to study the effect of starvation on isoproterenol cardiotoxicity. A series of experiments was performed to investigate this problem.

Experiment A. One hundred male rats of the Long Evans strain were used for this study. They were kept in a temperature- and humidity-controlled room and were allowed to take water ad libitum. The rats were divided in two groups. In Group I the animals were starved, whereas in Group II the rats were kept on a normal diet. On each of the last 2 days of the 6-day period of pretreatment, both groups were injected with 85 mg. per kilogram of isoproterenol HCl subcutaneously. The rats were then killed, autopsied, and the hearts weighed and fixed in Bouin's solution; frontal sections of the hearts were embedded in paraffin and stained with hematoxylin-eosin. The microscopic heart lesions were graded according to the system described previously.[8]

Table II shows the result of the experiment. It can be seen that starvation protected the rats against the isoproterenol toxicity. There was no mortality among the 50 starving rats and the heart weight as well as the severity of cardiac necrosis were markedly reduced.

Experiment B. Sixty male rats of the Long Evans strain were divided into six groups of 10 each. Group I was kept on a normal commercial diet. Group II received a low-potassium diet for 7 days. Group III had the same diet plus 0.5 mM of sodium chloride by gavage twice daily per rat. Groups IV, V, and VI received the same regimens as Groups I, II, and III, respectively, for 5 days, after which they received no food. In Group VI the adminis-

Table II. Effect of starvation on the cardiac necrosis elicited by two injections of subcutaneous isoproterenol, 85 mg./Kg.

Group	Number of rats	Body weight		Mortality	Relative heart weight	Microscopic heart necrosis
		Start	End			
Starved for 6 days	50	217 ± 4	181 ± 4	0	426 ± 7	1.66
Normal diet	50	219 ± 6	235 ± 3	4	534 ± 22	3.23

Table III. Effect of starvation and intake of salt on the myocardial necrosis produced by 85 mg./Kg. of isoproterenol given subcutaneously on the last 2 days of the experiments

Group	Body weight		Mortality	Relative heart weight	Microscopic heart necrosis
	Start	End			
Normal diet	208 ± 5	218 ± 4	1	460 ± 12	3.2
K-deficient diet	237 ± 4	223 ± 7	6	457 ± 27	3.8
K-deficient diet with additional Na	236 ± 6	240 ± 5	10	517	4.0*
Normal diet and 2 day starvation	279 ± 14	255 ± 10	0	403 ± 14	1.4
K-deficient diet and 2 day starvation	243 ± 7	212 ± 7	1	437 ± 14	3.3
K-deficient diet with additional Na and 2 day starvation	233 ± 6	207 ± 3	0	455 ± 18	3.4

*Data are based on the examination of 2 rats which survived more than 32 hours.

tration of sodium chloride was continued. Rats in every group received on the sixth and seventh days 85 mg. per kilogram of isoproterenol subcutaneously.

The results of the experiments are presented in Table III. It can be seen that the starvation of the animals from the fifth day of the experiment resulted in a marked reduction in the mortality after administration of isoproterenol. Whereas 1, 6, and 10 rats died in groups on a normal, a low potassium, and a low potassium and sodium-supplemented diet, only 1 rat died in the corresponding starvation groups. In the animals which died hemorrhagic lung edema and occasionally focal hepatic and renal necrosis were observed in addition to massive cardiac necrosis.

Histologic examination of the heart showed that the grade of cardiac necrosis was markedly reduced in fasting rats as compared to that in the rats maintained on a normal diet. The severity of myocardial necrosis on the potassium-deficient diets was, however, only slightly reduced by the starvation.

Atrial variety of isoproterenol myocardial necrosis

In rats on a potassium-deficient diet no correlation was found between the mortality rate and the microscopic grade of ventricular heart necrosis after the administration of isoproterenol. Although starvation of these animals from the fifth day of the period of pretreatment markedly reduced the mortality rate, the severity of ventricular myocardial necrosis was not significantly different from that in the nonstarved rats on a potassium-deficient diet.

To evaluate the cause of the discrepancy between the lethal and cardiotoxic action of isoproterenol, we re-examined the heart specimens from our previous studies. This investigation revealed that mineralocorticoids and DOCA not only augmented the severity of myocardial necrosis, as was

reported earlier[15,16] but also modified the heart changes in such a manner that atrial necrosis became predominant. The pathology and pathogenesis of this atrial variety of isoproterenol heart necrosis has since been reported in detail.[9]

Since in these studies a good correlation was found between the mortality rate and the severity of atrial necrosis, we attempted to see what effect, if any, the starvation had upon the severity of atrial necrosis when the administration of isoproterenol was preceded by various amounts of intake of salt in the diet.

As can be seen from Table IV, in this experiment a good correlation was found between the severity of atrial infarction and the mortality of rats given DOCA or on a low potassium diet followed by the administration of isoproterenol. Furthermore, it appears that the protection obtained by starvation in these rats is the result of the less severe involvement of the atria and not of the amelioration of the myocardial necrosis in general.

This finding indicates that the atrial infarction should not be regarded as of secondary importance, even though the consequences of ventricular necrosis seem to predominate.[20,21] Similarly to the results of our experiments, there are reports in the literature[22-25] in which the involvement of certain special areas of the heart muscle were found to be of paramount importance. It is possible that a similar situation may exist and be of clinical significance in certain cases of human coronary heart disease.[4,20] Involvement of the atria might be the explanation of the cause of death in some cases in which ventricular changes were insignificant. Since the atria are not extensively examined in routine postmortem examination, this lesion may be overlooked. The significance of atrial infarction and the pathomechanism by means of which electrolyte disturbance predisposes to the development and influences the localization of myocardial necrosis is currently being studied by us in both human and experimental material.

Table IV. Data indicating the correlation between the severity of myocardial necrosis and mortality rates

Group	Mortality	Grade of heart necrosis	
		Atrial	Ventricular
K-deficient diet	6	3.2	3.8
K-deficient diet with additional N	10	4.0	4.0
K-deficient diet with starvation†	1	2.0	3.3
K-deficient diet with additional sodium and starvation†	0	1.3	3.4

*Rats received 85 mg./Kg. of isoproterenol subcutaneously on the last (seventh and eighth) day of the experiments.
†Rats were starved from the fifth day of pretreatment period.

Modification of isoproterenol heart necrosis by pharmacologic means

The therapeutic suppression and long-range prevention of the sympathogenic biochemical trigger mechanism of anoxemic heart changes were recently surveyed by Raab.[26] There appear to be several methods which may counteract the effect of an excessive amount of catechols on the heart muscle.[27] The pharmacologic prevention of isoproterenol cardiac necrosis originated from Zbinden, who confirmed our former observations on the morphology of the isoproterenol myocardial lesion. He was successful[28] in reducing the severity of isoproterenol cardiac necrosis by monamino-oxidase (MAO) inhibitors, isocarboxazid (Marplan) and 1-benzyl-2(trimethylacetyl) hydrazine (Tersavid). Since MAO inhibitors do not alter other cardiovascular effects of isoproterenol, Zbinden[29] suggested that the inhibition of myocardial necrosis observed in the rats pretreated with MAO inhibitors was due to a decreased oxygen requirement of the heart muscle. By influencing oxidative processes, MAO inhibitors may alleviate the symptoms of clinical angina pectoris.[30-32] The foregoing explanation adds some support to the theory proposed by us concerning the pathogenesis of isoproterenol myocardial necrosis.[12,13]

Similar pharmacologic studies were performed by Bajusz and Jasmin with a MAO inhibitor derivative Nialamide and serotonin on isoproterenol cardiac necrosis. By rating the severity and incidence of the microscopic heart lesions, they ob-

Table V. The effect of factors upon the mortality rate and severity of isoproterenol myocardial necrosis

Factor studied	Mortality	Myocardial necrosis
Endogenous factors		
Breed		Sprague-Dawley [illegible] less sensitive
Age	↗	↗
Weight	↗	↗↗↗
Sex		
Hormones		
Premarin		
Estrone	↗	↗
Progesterone		–
Testosterone	↗	↗
Hyperthyroidism	↗↗	↗
Hypothyroidism	↙↙	↙↙↙
ACTH		
Adrenalectomy		
Glucocorticoid		
Mineralocorticoids	↗↗↗	↗↗↗
[illegible]		
High potassium diet	↙↙	↙↙↙
Low potassium diet	↗↗↗	↗↗↗
Low sodium diet	↙	↙↙
High sodium diet	↗↗	↗↗
Starvation	↙↙↙	↙
High fat and high carbohydrate diet (increased body weight)	↗↗↗	↗↗↗
Isolation stress	↗	↗
Pharmacologic agents		
MAO inhibitors	No data	↙↙

served marked protection with these drugs. According to their interpretation the mode of this protective action of MAO inhibitors is complex. They may act by liberating serotonin and the elevation of the level of serum serotonin in turn results in a coronary vasodilatation. This mechanism however can hardly be applied to explain the protective effect of these compounds in isoproterenol heart necrosis since isoproterenol is itself a coronary vasodilator.[36] Handforth suggested that isoproterenol cardiac necrosis is brought about by dilating pre-existing communication between coronary arteries and veins. This causes a bypass of blood from the capillary bed of the myocardium and subsequent ischemia and necrosis. It appears that further work to elucidate the pathogenesis of isoproterenol heart necrosis is required before the mode of the protective effect of antiadrenergic drugs can be assessed.

Summary and conclusion

An experimental method for producing myocardial necrosis of uniform severity in the rat by a synthetic adrenergic drug, isoproterenol, has been developed by our research group. The massive infarct-like necrosis was located most frequently in the apex and subendocardial portion of the ventricles.

We, along with others, have used isoproterenol-induced myocardial necrosis as a model for studying the effect of various endogenous and exogenous factors upon the development and severity of experimental myocardial necrosis.

Table V summarizes the factors studied. On the basis of the findings they may be divided into three categories. One group had no definite effect; this included sex, Premarin, progesterone, ACTH, glucocorticoids and probably the breed of animals. The second group protected the rats against the cardiotoxic effects of isoproterenol; this consisted of hypothyroid state, high-potassium diet, low-sodium diet, starvation, monoamino-oxidase inhibitor drugs (Marplan, Tersavid, Nialamide) and serotonin. The third group of factors increased the mortality rate and severity of myocardial necrosis with age, estrone, testosterone and isolation stress. In animals the aggravating effect was slight, whereas with increased weight, thyroxin, high-fat diet, and high-carbohydrate diet it was marked. Although there was also marked aggravation with mineralocorticoids, high-sodium diet, and low-potassium diet, in addition atrial necrosis became prominent when these factors were operating. Whereas in the animals which received mineralocorticoids or were on a high-sodium or low-potassium diet no definite correlation could be drawn between the severity of ventricular necrosis and the mortality [illegible] correlation existed between the severity of atrial necrosis and the mortality rate. This suggests that the severity of atrial myocardial necrosis has an important role in determining the out

come of acute myocardial infarction in the rat. The possibility that this may be of importance in regard to human pathology is the object of a study now in progress.

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Case reports

Selective angiocardiography in diagnosis of varicosity of the pulmonary veins

Report of a case

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Vari sity of the pulmonary veins is   ie of the rarer vascular abnormalities   the lungs. Most patients with this   d tion are asymptomatic and the lesion be mes apparent only after detection of   bnormal shadow in a thoracic roentgenogram. The exact anatomy of the anomaly a be demonstrated only by angiocardiography. The case comprising this report   nstitutes the third case to be diagnosed by angiocardiographic methods. The first description of the condition is usually attributed to Hedinger, Basel, who reported it at the fifth meeting of the German Pathological Society in 1907. In the earlier reports   this condition was encountered only a a postmortem entity. The condition has been diagnosed in vivo in 5 cases.   C mes and Horváth,[1] Hagen and Heinz   and Schulze   each have reported single cases n which the lesions were demonstrated by tomography. The cases of Mouqu and associates   and Gottesman and Weinstein   are the only ones on record in which the diagnosis has been made by means of angiocardiography.

Report of case

A 7 year-old girl   as seen   t the Mayo Clinic for evaluation of know   congenital heart disease. The only symptom had been d   pnea on exertion. Clinical examination suggested the diagnosis of   entricular septal defect   ith severe pulmonary hypertension   nd   significant increase in pulmonary blood flow. A   oentgenogram of the chest (Fig. 1) revealed several rounded shadow   i   the mid-portion of the right l ng,   hich   ere highly suggest   of multiple pulmonary arteriovenous fist la

Tomograph   of the right l ng demonstrated   large tortuous   essel   hich   ppeared t   represent   pulmonary   ein draining the right upper lobe (Fig. 2). This   essel coursed dow   rd and then medially, joining the heart   the usual sit   of juncture of the right superior pulmonary vein   ith the right border of the heart. A second large   essel cou sed parallel to and overlapped the right border of the heart. This   thought t   epresent   dilated   nferior pulmonary   ein.

Catheterization of the right side of the heart   nd selecti   ngiocardiography   ere then performed. The findings   cardiac   theterization   ere consi tent   ith the diagnosis of   entricular septal defect, patent ductus arteriosu , and severe pulmonary hypertension. Pulmonary   rterial pressure   95 per cent of the sy temic pressure   nd the ratio of pulmonary t   systemic flow   1.3

A select   ngi   rdiogram   made after the inject on f 27 ml. of 69 per   ent solution f radio-paque medium (Renogr   6 ml. per kilogram of

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Fig. 1. Thoracic roentgenogram.



Fig. 2. Tomogram of right lung.



Fig. 3. Angiocardiograms. a, Frontal view showing normal pulmonary artery branches. b, One third of a second later than a, showing pulmonary artery branches and a portion of the aortic arch opacified via patent ductus arteriosus. c and d, Frontal and lateral views made approximately 3 seconds later during phase of opacification of pulmonary veins and left heart, demonstrating large tortuous pulmonary veins in right lung. These veins are seen to communicate with the left atrium.

body weight) into the main pulmonary artery with simultaneous biplane anteroposterior and lateral film exposures being made at the rate of 6 films per second. The pulmonary artery and its branches were opacified first, and these vessels appeared to be slightly enlarged but otherwise normal (Fig. 3,a). At the time of opacification of the main pulmonary artery, a small amount of the contrast medium was seen to pass from the pulmonary artery to the arch of the aorta via a patent ductus arteriosus (Fig. 3,b). After filling of the pulmonary artery and pulmonary capillaries, the pulmonary veins were opacified. The pulmonary veins of the left lung were normal and entered the left atrium in the usual manner. The pulmonary veins of the right lung were grossly abnormal (Fig. 3,c,d). A large, dilated, and tortuous superior pulmonary vein appeared to drain the entire right upper lobe and the superior segment of the right lower lobe. The remainder of the right lower lobe drained into a dilated inferior pulmonary vein. Both the superior and inferior pulmonary veins entered the left atrium in a normal manner. It was evident that the dilated right pulmonary veins filled in a normal manner after the pulmonary artery and capillaries had filled. Thus, a direct pulmonary arteriovenous communication, as is present in pulmonary arteriovenous fistula, did not exist in this case.

Comment

Most patients who have varicosities of the pulmonary veins are asymptomatic and the lesions are discovered on roentgenographic examination of the thorax. The presenting feature in most cases is a rounded shadow in the lung due to the varicosity being seen end-on or tangentially; more rarely, a longer portion of the dilated pulmonary vein is visualized as an elongated or fusiform shadow. There is no predilection toward a particular site in the lungs.

From the thoracic roentgenogram the lesion may be erroneously diagnosed as a pulmonary arteriovenous fistula, pulmonary tuberculosis, or bronchogenic carcinoma. The vascular nature of the anomaly has often been suspected only when the lesion does not change in size or resolve after specific treatment, or when a change in size of a lesion is noted with the Valsalva and Müller maneuvers. Selective angiocardiography is the only method by which a definitive anatomic diagnosis can be made.

Summary

A case has been presented of varicosity of the pulmonary veins, an unusual vascular anomaly of the lungs. This is the twelfth such case reported and constitutes the third reported case in which the diagnosis was made by means of angiocardiography.

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A histopathologic study of the atrioventricular communications in a case of WPW with incomplete left bundle branch block

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The anatomic base of the Wolff-Parkinson-White syndrome (WPW) is today uncertain. To arrive at such a base, as previously pointed out, it is necessary to examine histologically by serial section the entire conduction system and the entire atrioventricular (A-V) junctions of many hearts with this syndrome. To date, only 5† such hearts have been examined in this manner.[1-4] This communication presents a sixth heart so examined.

Clinical review

This 50-year-old white woman had had attacks of paroxysmal tachycardia since early childhood, each attack had lasted about several hours. These could be brought on by abrupt motion, slight pressure on the chest, change in the weather, and excessive fatigue. They were controlled by elevating the feet against a wall, taking deep breaths, and sometimes by drinking a glass of milk, or going to stool. Either aromatic spirits of ammonia or quinidine shortened the attacks. The attacks were followed by marked weakness for an hour or even a day. However, for the last 4 years the patient had had difficulty in controlling the attacks. In the last year before death she complained of precordial pain of short duration, unrelated to physical exercise, and she had dizzy spells without losing consciousness.

Two brothers had died from heart disease of unknown origin, and her father had died from arteriosclerotic heart disease when he was 70 years old. The patient, her father, and 3 brothers were alcoholics. The patient drank 1 pint to 1 quart of alcohol per day periodically and alternately abstained from alcohol. She was a heavy cigarette smoker. She had had polyarthritis for 7 months when she was 34 years old, and had undergone a left radical mastectomy for cystic disease when she was 48.

Physical examination revealed the following: The blood pressure was 140/80 mm. Hg, and the pulse was 75 to 80 per minute between attacks. The heart sounds were normal and no murmurs were heard. X-ray examination showed slight left ventricular hypertrophy. A diagnosis of WPW was first made 6 years before her death. Electrocardiographic examination made 2 years before death revealed WPW of the B type, with incomplete left bundle branch block (Fig. 1).

The patient was treated with Pronestyl during attacks of paroxysmal tachycardia, quinidine for a short period after the attacks, and then potassium chloride for 6 months.

After drinking two bottles of whiskey in the

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†Note: In a previous communication, one of us (M.L.) erroneously stated that there were at that time 4 cases of WPW in which both the conduction system and the atrioventricular rims were serially sectioned. We overlooked the case of Dreifuss and associates. In a personal communication, Dr. George Burch has informed us that in the case study of both the conduction system and the atrioventricular rims was carried out, and the conduction system was found to be normal.

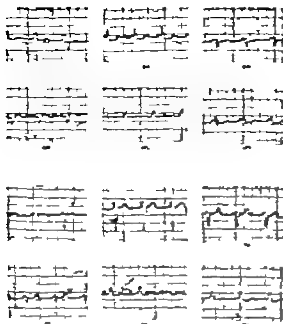


Fig. 1. Electrocardiogram taken 2 years before death, showing WPW of the B type with incomplete left bundle branch block.

of one of one night, she had an uncontrollable attack of paroxysmal tachycardia and died.

Postmortem examination. Postmortem examination was limited to the heart.

GROSS EXAMINATION. The heart weighed 505 grams, fixed. Both atria were hypertrophied. The right ventricle was hypertrophied and dilated, and the tricuspid and the pulmonary orifice and the pulmonary trunk were dilated. The left ventricle was a small chamber with an atypical configuration of papillary muscles, with the posterior papillary muscle anchored on the angle between the septum and posterior wall. There was marked narrowing of the first 2 cm. of the right main coronary artery and of the left circumflex artery, and there were multiple spots of marked narrowing throughout the course of the left anterior descending artery. An old scar was present at the base of the ventricular septum. The aorta emerged from the left ventricle in a somewhat oblique manner.

HISTOLOGIC EXAMINATION. Both entire atrioventricular junctions and the entire conduction system, with the exception of some of the peripheral branches of the left bundle branch, were cut into blocks and serially sectioned. All the sections of the right A-V junction, the left A-V junction in the region of the aorta, and the sinoatrial node, the pre-A-V nodal area, the A-V node, the A-V bundle, and the upper part of the bundle branches were retained. Every tenth section of the remainder of the left A-V junction and of the lower bundle branches was retained, and every fortieth section of the atrial septum between the sinoatrial and A-V nodes was retained. The conduction system was cut at 10 μ, whereas the A-V junctions were cut at 15 μ. All sections were alternately stained with hematoxylin-eosin and Weigert van Gieson stain. A total of 23,[illegible]40 sections were thus examined.

Right atrioventricular junction. There was a distinct communication between atrium and ventricle subendocardially in the superior part of the free walls, measuring 1.3 mm. in width (Fig. 2). This communication consisted of muscle cells which were larger than normal, but which were not typical Purkinje cells. These cells showed degenerative changes with fibrosis.

Left atrioventricular junction. No communications between atrium and ventricle were found at this junction.

Conduction system. All parts of the conduction system showed marked fatty infiltration, with elastosis and a slight infiltration of mononuclear cells. The ganglion cells about the sinoatrial node showed fibrosis with degenerative changes. Between the junction of the A-V node and bundle and the right atrial musculature there was a small communication which consisted of typical atrial muscle cells (Fig. 3). Mahaim fibers were present at the junction of the node and bundle, and the penetrating portion of the bundle and the ventricular myocardium. The bundle shifted toward the left side as the posterior radiation of the left bundle branch commenced (Fig. 4, *top*). The beginning of the posterior and anterior radiations of the left bundle branch overlay the infarct of the septum described below (Fig. 4). Its fibers were very slender, being thinner than myocardial fibers, with slender nuclei and cytoplasm as eosinophilic as myocardial cells. Below the infarct they became typical Purkinje cells. The right bundle branch revealed no change aside from the changes described for the entire conduction system.

Myocardium in general. The base of the ventricular septum presented an old scar about 2 cm. long which extended from the posterior wall anteriorly and involved both the right and left sides of the septum (Fig. 4, *bottom left*). This infarct involved the beginning of the left bundle branch as described above. The entire atrial and ventricular myocardium showed an increase in elastic and fat tissue, with perivascular fibrosis, fibrosis of ganglion cells, and a slight infiltration of mononuclear cells. Focally present were small muscle cells which looked almost like macrophages. The mitral annulus was hyalinized and focally calcified. Zones of calcification were also present at the base of the ventricular septum and in the "pars membranacea," which in this case was replaced by muscle. The tricuspid annulus at the junction of the ventricular septum and anterior wall likewise showed zones of calcification. The fat tissue of the A-V grooves and of the epicardium showed likewise a fine infiltration with mononuclear cells, with elastosis and perivascular fibrosis and nerve cell fibrosis. The anatomic diagnoses were: (1) Communication between the right atrium and ventricle outside the conduction system. (2) Communication between the junction of the A-V node and bundle and the right atrium. (3) Arteriosclerotic heart disease. (A) old infarct of base of the ventricular septum; (B) atrophy of the origin of the left bundle branch; (C) focal calcification of the cardiac skeleton. (4) Elastosis, fatty infiltration, and mild chronic inflammation of the conduction system and

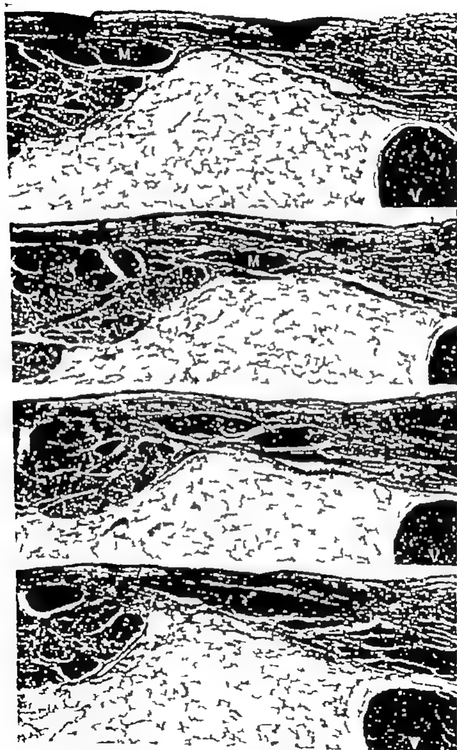


Fig. 2. Histologic sections of muscular communication between the right atrium and right ventricle. The communication is followed from atrium to ventricle (*from top to bottom*). Hematoxylin-eosin stain. ×56. *V*, Ventricular musculature. *A*, Atrial musculature. *M*, Muscular communication.

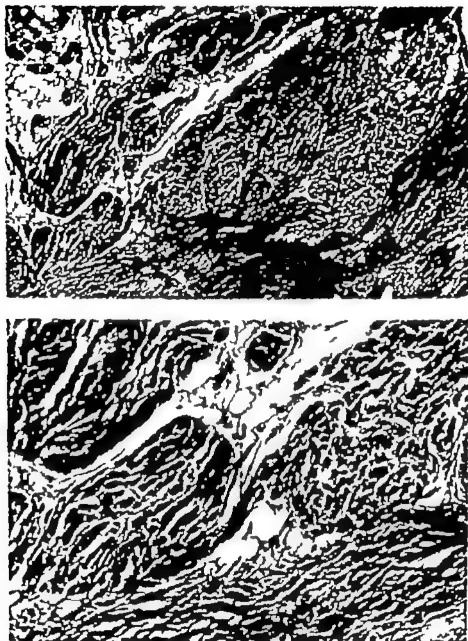


Fig. 3. Muscular communication between junction of A-V node and bundle and the right atrium. Hematoxylin-eosin stain; *above* ×60; *below* ×180. *N*, Distal part of node. *A*, Atrium. *J*, Junctional tissue. *C*, Central fibrous body.

of the myocardium. (5) Fibrosis of the ganglion cells of the heart. (6) Hypertrophy of both atria and right ventricle.

Discussion

The Wolff-Parkinson-White syndrome in this case may be considered to be congenital in view of the presence of paroxysmal tachycardia since early childhood. Therefore, if an anatomic change is to be correlated with this syndrome, then it must be in the communication between the right atrium and ventricle outside the conduction system. It is unlikely that the communication between the junction of the A-V node and bundle and the right atrium which bypasses the A-V node is related to this syndrome because (1) this connection has been seen by one of us (M.L.) in normal hearts, (2) in WPW

of the B type the activation starts in some portion of the right ventricle and (3) the QRS complex would be expected to be normal if the activation followed the normal pathway after this junction. The arteriosclerotic heart disease cannot be considered to be related to the WPW in this case, and the elastosis and perivascular fibrosis may be ascribed to the repeated attacks of paroxysmal tachycardia or perhaps to the alcoholism, or to both.

The anatomic evidence in favor of the various hypotheses for WPW have been reviewed previously. It is perhaps significant that of the 6 cases in which complete studies of the conduction system and

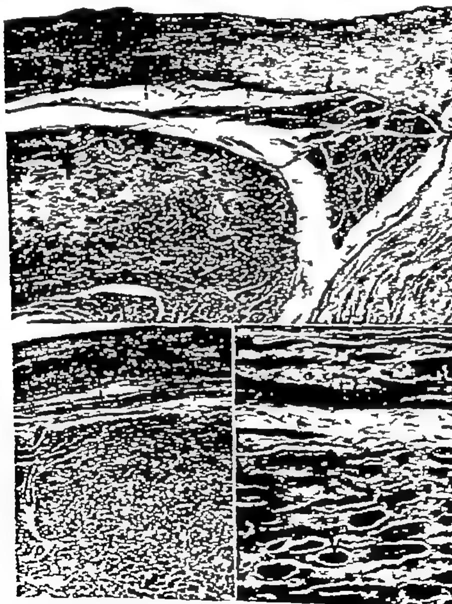


Fig. 4. Origin of left bundle branch and its relationship to the infarct. Hematoxylin-eosin stain. *Top*, A-V bundle and beginning left bundle branch. ×6. *Bottom left*, LBB fibers more distally. ×65. *Bottom right*, Purkinje fibers as compared to ventricular myocardium. ×75. *A-V*, A-V bundle. *LBB*, Fibers of left bundle branch. *V*, Ventricular myocardium. *I*, Infarct. *PK*, Purkinje fibers.

of the atrioventricular orifices have been made, communications outside the conduction system have been found in 5.

The combination of WPW with bundle branch block has been previously noted and discussed.[6] A diagnosis of incomplete left bundle branch block was suggested in our case because the beginning of the QRS was slightly superimposed on the downstroke of the P wave. In this type of minor superimposition of the QRS on the P wave a very slight aberrancy of the QRS is expected. In our case, marked aberrancy of the QRS is present, which suggests some degree of left bundle branch block in addition to the WPW syndrome.

As to the anatomic base of the incomplete left bundle branch block, atrophy of the origin of the left bundle branch was related to a basilar septal infarct produced by marked narrowing of all three main branches of the coronary arteries. It is interesting that there did not appear to be a complete interruption of continuity of the left bundle branch but marked atrophy of its cells. An ischemic pathogenesis in left bundle branch block is less common than mechanical interruption produced by degenerative changes in the pars membranacea, the annulus of the mitral valve, and the top of the muscular ventricular septum. Such changes were also present in our case, but the changes in the left bundle branch were seen to be related to the infarct.

Conclusion

Both entire atrioventricular junctions and the entire conduction system, with the exception of some of the peripheral branches of the left bundle branch, were serially sectioned in a case of Wolff-Parkinson-White syndrome with incomplete left bundle branch block. A communication outside the conduction system was found between the right atrium and right ventricle. A communication between the junction of the A-V node and bundle and the right atrium was also present. If an anatomic change is to be correlated with WPW, reasons are given why the junctional tissue between the right atrium and right ventricle may be of significance. The incomplete left bundle branch block was found to be correlated with atrophy (but not complete destruction) of the left bundle branch.

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Congenital aneurysms of the ventricular septum

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Congenital aneurysms of the ventricular septum are uncommon anomalies and are seldom associated with clinical manifestations. Few cases have been reported in the literature, and in only one of them was the lesion recognized during life. As far as we can ascertain, no operatively treated case has been recorded. For these reasons we have been prompted to review the pertinent literature briefly and to report a case diagnosed preoperatively and treated successfully by open repair.

Case report

The patient had been seen in the outpatient clinic at the age of 6 years because of the presence of a cardiac murmur. He had had two episodes of pneumonia during the first months of life, and it was at that time that the family was first told that a heart murmur was present. The father stated that when his son was an infant the cardiac murmur could be heard at some distance in a quiet room by members of the family. At the time of his initial examination the boy was somewhat small for his age. A strong systolic thrill was felt over the entire precordium and a loud systolic murmur was heard, most prominently in the fourth left intercostal space. The electrocardiogram was essentially normal, and fluoroscopic and x-ray studies suggested slight right ventricular enlargement. A ventricular septal defect was considered to be the most likely diagnosis. In September, 1958, he had been rather ill with some infectious process, and at that time the question of subacute bacterial endocarditis arose.

He was admitted to the hospital in 1959 at the age of 12 for cardiac catheterization and cineangiographic study. He appeared to be in good health. Nothing abnormal was noted except for a systolic thrill and murmur. During cardiac catheterization it was possible to pass the catheter from the right atrium into the left atrium via a patent foramen ovale and into the left ventricle. Pressures were normal in all four chambers and there was no definite evidence from oxygen saturation studies of any shunt (Table I). Cineangiograms revealed an aneurysm in the region of the membranous portion of the ventricular septum and a left-to-right shunt through it (Fig. 1).

Operation was carried out on Sept. 4, 1959, with total cardiopulmonary bypass. When the right ventricle was opened, an aneurysm was seen in the membranous portion of the septum. It bulged into the right ventricle with each ventricular systole, was 12 or 13 mm. in diameter at the base, and had a small defect in the dome approximately 3 mm. in diameter. No vegetations were seen. The aneurysm was opened widely by incising its wall from the margins of the defect toward the base. The fibrous tissue at the base of the aneurysm was brought together with a continuous mattress suture so as to close the defect in the septum. This closure was further buttressed by oversewing the wall of the aneurysm with simple Lembert sutures. The patient made an uneventful recovery and was discharged from the hospital 8 days later.

He has remained quite well. In April, 1962, an electrocardiogram was essentially normal, and x-ray studies revealed a normal-appearing heart. Some regression in cardiac size had occurred since operation. When last seen on Aug. 31, 1962, the patient was without symptoms. He was growing normally and was extremely active, participating in hiking, wrestling, hunting, and other activities. The heart was not enlarged to percussion, the rate and rhythm were normal, no thrill was palpable, and no murmur was heard. The second pulmonary sound was normal in intensity.

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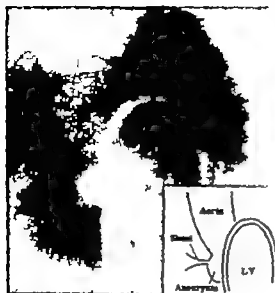


Fig 1 Photogr ph of one frame of the ineangio-graphic study made the left terior oblique pro-jection showing filling of the neurysm and shunting of contrast material through it into the right ven-tricle For the sake of larity the details are outlined schematically n the sert The catheter has been passed in foramen ovale nd the left trium int the left entricle

Review of the literature

Congenital aneurysm of the ventricular septum occurs infrequently Abbott s tabulation of 1 000 cases of congenital heart disease includes only 7 instances in which it occurred as the sole anomaly and 9 others in which it was associated with other congenital cardiac abnormalities It is not mentioned in Taussig s comprehensive treatise Up until 1957 approximately 80 cases had been reported [3] and not many have appeared in the literature since then. The first description of a ventricular aneurysm is attributed to Laennec in 1826 [4]

Some of the early authors thought that these lesions occurred as the consequence of bacterial endocarditis Mall recognized their congenital nature and proposed a theory of origin in 1912. In describing the findings in one such heart he noted that the membranous septum was too far to the left." When the ventricle was viewed through the aorta the membranous septum appeared to be almost parallel to the plane of the aortic ring rather than perpendicular to it There was no evidence of endocarditis. He was led to postulate that these lesions could be traced to an embryonic arrest of development in which the "inferior septum did not move to the right sufficiently far but remained within the vestibule of the aorta A number of observers have lent support to the hypothesis. Cannell[6] studied 2 patient one a 24-year-old man who died of pneumonia and the other a 60-year-old man who died from post operative peritonitis, in both of whom the aorta appeared to be directed toward the right ventricle In both the muscular septum protruded into the aortic vestibule and the membranous septum was almost horizontal instead of vertical In 1936 and 1938 Lev and Saphir[4,7] described 2 cases of aneurysm of the ventricular septum in the hearts of Mongoloid infants, reviewed the literature extensively and examined various theories concerning the origin of these aneurysms. They thought that Mall s concept of an abnormal shift of the septum was basically correct and they amplified this theory to include faulty rotation of the aorta According to their interpretation the anomaly is really a very mild form of transposition. The failure of the aorta to shift far enough to the left and of the septum to shift far enough to the right results in an overriding aorta and a deformed vestibule so that the mem-

Table 1 Catheterization data

	Pressure (mm. Hg)	Oxygen content (ml %)
Left pulmonary ein	3 6	15 29
Left atrium	3 6	15 38
Right pulmonary vein	7 5	
Right trium	1 5	12 20
Inferior vena cava	2 7	11 79
Inferior vena cava with hepatic pressure	2 5	
Superior ena cava	2 7	11 08
Superior ena cava with hepatic pressure	2 7	
Right entricle pex	24 5/3 5	11 94
Right pulmonary artery		11 68
Main pulmonary artery	23 3/4 2	12 11
Right ventricle, outflow tract	26 3/3 5	11 77
Left entricle	109 5/5 5	
Capacity		16 12

branous septum is oblique or horizontal in position. These features seem to be present in all instances in which a search for them has been made.

Although many of the patients reported on have been without cardiac complaints this has not always been so. It is clear that in many of the latter cases the symptoms have been attributable to associated cardiac difficulties rather than to the aneurysm itself. For example Masug[9] described a patient with an aneurysm of the ventricular septum who died at the age of 49 with severe coronary artery disease. Rae reported the case of a 63-year-old man who died of pulmonary embolism and who had been in heart failure for a year. He was found to have subaortic stenosis in addition to the ventricular septal aneurysm. Furthermore, the aortic valve leaflets were deformed and there were vegetations of chronic and acute bacterial endocarditis on the cusps. Neither the aneurysm nor the subaortic ring appeared to harbor bacterial vegetations. In Leckert and Sternberg's patient the ventricular septal aneurysm was discovered as an incidental postmortem finding. The patient had died of congestive failure secondary to aortic insufficiency. One of the 2 patients reported on by Rogers and his associates[11] was thought possibly to have had symptoms referable to the lesion. He was a 70-year-old man with hypertensive cardiovascular disease of 10 years duration. He had had intermittent episodes of arrhythmia of various sorts, including paroxysmal atrial tachycardia and idioventricular rhythm. On postmortem examination however coronary sclerosis was also found to be present. On the other hand Clark and White[12] reported the case of a 47 year-old man who died after a series of Stokes-Adams attacks, in whom the only significant finding at autopsy was an aneurysm of the ventricular septum. He had shown alternating runs of ventricular flutter, ventricular tachycardia, ventricular standstill and complete A-V dissociation. Microscopic examination of the aneurysm revealed relatively acellular collagenous tissue and no structures resembling the bundle of His.

In some instances thrombi have been observed within the sac of the aneurysm. They could constitute a source for possible emboli. In most of the cases recorded in the literature, rupture of the aneurysm has not occurred nor has there been a developmental defect in the wall of the aneurysm. In some cases, as in ours, however this feature has been present. The aneurysm may bulge into the right ventricle as it did in our patient, or it may bulge into the right atrium as was true of Mall's case. Similarly rupture may occur into the right atrium as well as into the right ventricle. Indeed among the early reports is the case of Rokitansky[13] which was an instance of rupture into the right atrium.

We have found only one instance in which the diagnosis was made during life. In 1957 Steinberg[7] described a 60-year-old woman who had been noted to have increased pulsations of the pulmonary artery and questionably abnormal right hilar shadows on fluoroscopic examination and in whom an angiocardiogram disclosed an aneurysm of the ventricular septum. At the time of the report she had not developed cardiac symptoms during a 5-year period of observation.

Summary

Congenital aneurysms of the ventricular septum occur uncommonly. They apparently result from faulty shift of the septum and failure of proper rotation of the aorta according to the theory originally advanced by Mall and later amplified by Lev and Saphir. Although many patients are without cardiac complaints, some with aneurysms of the ventricular septum do have symptoms. Often such symptoms are related to associated defects, such as aortic insufficiency or to rupture of the aneurysm. Various disturbances in rhythm may occur and may be responsible for the death of the patient. Thrombi may be present and may give rise to embolic phenomena. The aneurysm may rupture into the right ventricle or into the right atrium. In our case the history of a thrill and bruit since the first few weeks of life suggests that the defect in the dome of the aneurysm was developmental rather than the result of later rupture.

A case of aneurysm of the ventricular septum associated with a small left-to-

right shunt through a defect in it has been described. The correct diagnosis was established by cineangiography and corrective surgery was carried out successfully.

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Review

Current concepts concerning the etiology of essential hypertension

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Since hypertension was identified as a distinct disease at the turn of the century, there have been many occasions when it seemed likely that its cause had been found, but each time it has proved illusory, and at present no one theory seems more promising than another. Some investigators indeed believe that ultimately the disease will be attributed to multiple interrelated factors as expressed in the mosaic theory of Page. Others regard hypertension not as a disease but as an expression of a graded physical characteristic. High blood pressure would then be analogous to exceptional height.

Population studies

The theory that hypertension is not a specific disease, forcefully presented by Pickering, is based upon three findings in surveys of blood pressure in the human population: (1) the distribution of blood pressure values in the population, (2) the effect of age upon blood pressure, and (3) the similarity in blood pressure levels among close relatives. Essential to this theory is the smooth distribution curve of blood pressure in the population. The blood pressure rises with age, and the slight skew in the distribution curve becomes more pronounced with increasing age, but a departure from this distribution pattern which would indicate the emergence of a group of subjects with a "disease" hypertension cannot be demonstrated at any stage. Attempts have been made to show that the change in the form of the distribution curve with age conceals a group of patients with essential hypertension, but it has been explained that technical deficiencies in blood pressure recording which are caused by the tendency to aggregate readings about the nearest ten millimeter mark are responsible for some irregularities in the distribution curves. This pitfall can be avoided, and recent studies show that a break in the blood pressure distribution curve cannot then be demonstrated. Furthermore, the separation of normal subjects from those with hypertension on the basis of blood pressure readings alone is shown to be artificial by the gradual increase in mortality experience from below "normal" to the highest levels as demonstrated by life insurance data.

A rise in blood pressure with age has been a consistent finding from the earliest population surveys, but the crucial evidence required by Pickering's theory is that the rise in pressure be found in the majority of individuals. Follow-up studies by Stamler[4] show this trend in only approximately one half the population, and data from life insurance companies demonstrate it in only one third of the population. Further evidence eventually will clarify this point, but

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normal or there may be some other anatomic change in the blood vessels

It has been of special interest that the various types of secondary hypertension chronic glomerulonephritis renovascular disease or aldosteronism have each demonstrated the same inability to relax fully during reactive hyperemia again suggesting that these several conditions may affect the blood vessels in the same way[22]

Conclusion

To form an opinion concerning the etiology of essential hypertension from the present evidence is difficult not because of the paucity of facts but rather because of the apparently equal strength of the rival theories. The possibility which would account for the greatest number of known facts is that essential hypertension is primarily a renal disease which results, either directly or through the intervention of the adrenal cortex in the abnormal handling of sodium water or possibly some other electrolyte This in turn leads to an increase in peripheral resistance either actively through changes in the contractile properties of the vascular smooth muscle or passively by decreasing the lumen of the vessels perhaps by cellular swelling as suggested by Tobian[22] Since this speculation involves a chain of events it would seem reasonable to propose that there may be a variety of causative mechanisms affecting the system at different points and/or that there is probably more than one means of producing the postulated metabolic abnormality

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Fundamentals of clinical cardiology

Current treatment of hypertension with drugs

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Since the first written description of hypertensive disease over forty five centuries ago as recorded in *Huang Ti Nei Ching Su Wên* (The Yellow Emperor's Classic of Internal Medicine)[1] in which is written ". . . In order to examine whether Yin or Yang predominates one must distinguish a gentle pulse and one of low tension from a hard and bounding pulse . . ."† considerable progress has been made in the treatment of primary or essential hypertension. Despite this long known history of hypertensive disease and its natural course, Smirk[2] as recently as 1961, in an effort to dispel all remaining doubts, questioned the rationale for antihypertensive therapy. He concluded that antihypertensive therapy is indicated in *all* cases of primary hypertension since it is associated with a reduction in mortality and morbidity.

Initially, there was general agreement that antihypertensive drugs prolonged the life of patients with accelerated hypertension[3-5] and reduced the incidence and severity of the associated signs, symptoms, and complications such as cardiac enlargement, exudative retinal changes with hemorrhages, and abnormal electrocardiograms.[11-14, 28] In recent years, reports have appeared which demonstrate that antihypertensive drugs reduce the mortality and ameliorate the manifestations of the disease in patients with benign primary hypertension.[7,8,29-46] Life insurance statistics furthermore demonstrate increased mortality in subjects with either increased systolic or increased diastolic blood pressure and an even greater increase in mortality when both systolic and diastolic blood pressures are concomitantly elevated.[47] There is good support, therefore, for the view that treatment with antihypertensive drugs should be instituted in all subjects with primary hypertension and it is the purpose of this report to review recent developments in the treatment of primary hypertension with drugs.

Objectives of antihypertensive drug therapy

Antihypertensive drugs are administered in the absence of specific contraindications until the desired therapeutic effect is achieved or until toxic symptoms appear. Symptoms of hypotension usually appear initially when the subject is in the standing posture and this "trough blood pressure" frequently determines the magnitude of reduction in blood pressure which

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†Yin—female (passive); Yang—male (active).

the patient can tolerate while continuing a useful and productive life. Although the severely hypertensive subject frequently experiences symptoms of hypotension as antihypertensive drugs reduce the blood pressure to normal levels,[8] with encouragement many of these subjects are able to lead productive lives at reduced levels of blood pressure which they were unable to tolerate several weeks or months previously.

The treatment with antihypertensive drugs of the hypertensive patient who has renal insufficiency presents additional problems since the combination of renal insufficiency and hypertension is usually ominous.[14] Life expectancy is rarely more than 6 months in untreated subjects with rapidly progressive renal insufficiency and hypertension.[14] Approximately 50 per cent of all patients with accelerated hypertension enter the hospital with azotemia[15] and 30 per cent enter with frank uremia.[16] A tangible result of therapy with antihypertensive drugs has been a significant decrease in mortality in patients with accelerated hypertension and azotemia.[15-18] Most clinics agree that hypertensive patients who have determinations of blood urea nitrogen (BUN) of less than 70 *mg. per cent* without additional complications have a reasonable survival rate; when the BUN is between 70 and 100 *mg. per cent* the response to antihypertensive drug therapy is variable and when the BUN is over 100 to 150 mg. per cent the prognosis is poor.[15, 16, 18, 19]

Patients with slow progression of renal insufficiency, azotemia, and hypertension compose the major group of subjects with renal insufficiency and hypertension.[20] Substantial data from many clinics[8, 19-21, 23, 24] indicate that antihypertensive therapy may prevent progressive renal insufficiency and that these patients have an increased life expectancy with little morbidity except for perhaps a slight elevation of the BUN. Most clinics do not attempt to achieve normotension when the BUN slowly rises although others[14] suggest that normotension must be achieved for optimal results.

The object of antihypertensive drug therapy in patients with hypertension and acute or slow deterioration of renal function is the maximum reduction of the blood pressure *toward normal* without aggravation of the renal insufficiency. The flexibility of antihypertensive drug therapy which permits a lowering of the blood pressure and maintenance of adequate renal function is a major advantage of chemotherapy. With the exception of hydralazine and alpha-methyl dopa, all current antihypertensive drugs lower renal blood flow and glomerular filtration rate concomitant with their antihypertensive effect, and there is a direct correlation between the alteration in renal hemodynamics and the reduction in blood pressure.[14] Hydralazine, which has been used extensively in treating patients with hypertension and renal insufficiency, is unique and particularly suitable because it increases cardiac output, renal plasma flow, and glomerular filtration rate in acute experiments, and with chronic therapy, although increased blood flows are not observed, there is no evidence that it actually lowers renal plasma flow.[25]

The antihypertensive drugs which are employed currently fall into the following categories: (1) benzothiadiazine and phthalimidine diuretics, (2) guanethidine and bretylium tosylate, (3) ganglionic and adrenergic blocking agents and the Veratrum alkaloids, (4) hydralazine, (5) *Rauwolfia serpentina* derivatives, (6) decarboxylase inhibitors, (7) monoamine oxidase inhibitors, (8) aldosterone antagonists.

Benzothiadiazine and phthalimidine diuretics

The structure of chlorothiazide has been altered during the past several years, and these modifications have yielded many congeners which comprise the thiazide diuretic group. The benzothiadiazine ring has been modified at the second, third, fourth, and sixth positions. When the double bond at the third and fourth position is saturated with two hydrogen atoms, the hydrogenated group of thiazides is produced and *the dose range is reduced by one tenth*. The effective dose range of the *hydrogenated group (hydrochlorothiazide and hydroflumethiazide)* is 20 to 200 mg., and *doses greater than 200 mg. have no further saluretic effect*.[26] Flumethiazide and hydroflumethiazide have been prepared by the

replacement of the chloride atom at the sixth position by a trifluoromethyl group in the chlorothiazide and hydrochlorothiazide structures, respectively. Both chlorothiazide and flumethiazide have a double bond at the third and fourth positions and are employed in a dosage range of 200 to 2,000 mg. daily. Sodium and chloride are excreted equally with chlorothiazide and flumethiazide, whereas chloruresis is usually greater than natriuresis with the hydrogenated drugs. Modifications of the hydrogenated group at position three have resulted in additional clinically useful drugs. Substitution of a trichloromethyl group at position three of hydrochlorothiazide results in trichloromethiazide, and substitution of a benzyl group at position three of hydroflumethiazide results in benzhydroflumethiazide. Substitution of a methyl radical at position two and a chlormethyl group at position three of hydrochlorothiazide results in methyclothiazide, whereas substitution of a benzylthiomethyl group at position three of chlorothiazide results in benzylchlorothiazide. These drugs, which have an additional group at the third position (trichlormethiazide, benzhydroflumethiazide, and methyclothiazide), are employed in a maximum dosage of 10 mg., which is 0.5 per cent of the chlorothiazide dose. All of these thiazides can be used interchangeably and they have equivalent effects on the excretion of the sodium when employed in maximum dosage.

The thiazide drugs are powerful diuretic agents which have an evident diuretic and saluretic action approximately 2 hours after oral administration and continuing for 10 to 30 hours. The pharmacologic effect of the diuretic and saluretic action of the thiazides is exerted at the proximal and distal renal tubules. They have no acute effect on renal blood flow or glomerular filtration rate, although after chronic administration they may decrease renal blood flow and glomerular filtration concomitant with a decrease in circulating plasma volume.

The mechanism of the hypotensive effect of thiazide drugs is unknown. Although it has been demonstrated that a reduction in plasma volume and cardiac output is responsible for the moderate hypotensive effect initially, it has also been demonstrated that the hypotensive effect persists despite correction of the hypovolemia by infusion of saline. Furthermore, after the prolonged administration of thiazide diuretics, plasma volume returns to levels that were present before treatment. A decrease in the initially high reactivity of the digital blood vessels to l-norepinephrine in the hypertensive subject has been noted with sodium depletion, thus providing a clue to the mechanism of action of the thiazides. Other observers have similarly implicated altered sodium ion gradients, decreased responsiveness to (infused) norepinephrine, and decreased action of vascular smooth muscle.

The phthalimidine drugs are potent diuretic and antihypertensive agents similar to the benzothiadiazine agents. Chlorthalidone has a saluretic action similar to the thiazide drugs but of longer duration. The duration of action of the natriuretic effect of chlorthalidone may be 48 hours, in contrast to that of chlorothiazide, which is rarely longer than 12 to 18 hours. An antihypertensive effect with chlorthalidone, therefore, may be achieved with a daily dose of 100 to 200 mg. for 2 weeks, followed perhaps, by a daily dose of 100 to 200 mg. every second day.

Brest and Moyer have summarized the advantages of the thiazide drugs in the treatment of hypertension as follows: (1) the thiazides are potent and effective orally, (2) tolerance rarely develops, (3) toxic and side effects are rare, (4) electrolyte imbalance is unusual, (5) the thiazides potentiate other antihypertensive drugs.

When the thiazide drugs are used continuously rather than intermittently, the antihypertensive effect is maximum. Rigid restriction of salt is not recommended and a daily intake of 4 to 5 Gm. of sodium chloride is needed. Not infrequently, prophylactic supplements of potassium are required. The blood pressure usually returns to pretreatment levels after the oral administration of thiazide drugs has been discontinued.

Side effects and toxic symptoms are rarely observed with the thiazide diuretics. The incidence is approximately the same with each of the benzothiadiazine drugs.

Mild gastrointestinal distress, weakness and easy fatigability have been described In a small number of patients, maculopapular petechial or purpuric eruptions have been encountered The purpura may or may not be associated with thrombocytopenia Hyperglycemia has been reported Clearance of uric acid is decreased and hyperuricemia is not infrequently observed Acute gouty arthritis may occur and require treatment with colchicine or probenecid if it is elected to continue thiazide drug therapy There have been no reports to date implicating chronic subclinical hypokalemia associated with thiazide drug therapy as a cause of hypokalemic nephropathy The BUN may be elevated after the administration of thiazide drugs, and in patients with renal insufficiency these agents must be administered with caution Azotemia usually occurs in subjects with reduced renal function and is probably related to the reduced renal blood flow

In addition to the antihypertensive effect of the thiazide drugs, these compounds are particularly useful in combination with other antihypertensive agents. They potentiate the effectiveness of many such drugs, including the *Rauwolfia serpentina* derivatives, guanethidine, hydralazine and the ganglionic blocking compounds.[66-67]

Guanethidine

Since the therapeutic effectiveness of guanethidine in the treatment of hypertension was demonstrated 3 years ago [69, 71] numerous reports have appeared confirming these results.[71] After the administration of guanethidine there is a blockade of efferent sympathetic pathways[4] which is apparently related to a reduction in the tissue concentration of the neurohumoral transmitter norepinephrine This has been demonstrated in the hearts and aortas of animals by several groups of investigators.[73-81] Guanethidine therefore in effect produces a chemical sympathectomy [69] There is no evidence that guanethidine produces ganglionic blockade and the absence of parasympatholytic effects eliminates disturbing side actions. Moreover guanethidine has no significant effect on afferent or central segments of sympathetic reflex arcs or on vascular smooth muscle.[69]

After the oral administration of guanethidine an antihypertensive effect is not observed for 48 to 72 hours—the hypotensive effect moreover may persist after discontinuation of the drug for a relatively long period of time and not infrequently for 7 to 10 days.[84] For this reason the drug may be administered orally as a single daily dose

The maximum effect of guanethidine is achieved by careful adjustment of dosage. Therapeutic responses may be checked after the daily administration of 5 to 10 mg in patients with mild hypertension More commonly however an initial daily dose of 20 to 25 mg is selected and the dosage is increased at weekly intervals by increments of 10 mg The antihypertensive effect is more profound when the subject is in the erect position than when he is in the recumbent position as with ganglionic blocking drugs and the blood pressure should therefore be titrated with the patient erect Since the clinical results with guanethidine are at least equal to those of the ganglionic blocking agents which previously were the most potent antihypertensive drugs, the absence of parasympatholytic and other side effects with the administration of guanethidine would appear to support claims for the superiority of this compound in the treatment of hypertension

Dizziness and orthostatic weakness are the most frequently observed untoward effects of guanethidine and can be reduced or abolished by a reduction in dosage of the drug Diarrhea usually manifested by frequent bowel movements rather than loose stools, and failure of ejaculation in male patients without impotence are side effects which are also observed The administration of ganglionic blocking drugs to guanethidine-treated subjects in an attempt to ameliorate the diarrhea and enhance hypotensive effectiveness has not proved to be successful.[84] However the individually adjusted combined administration of a thiazide diuretic and guanethidine does reduce the dosage of guanethidine and lowers the incidence of side effects.[84] Therefore the advantages of guanethidine are (1) effective potency as an antihypertensive agent (2) absence of parasympathetic blockade side effects, and (3) con

venient daily dosage. It is not unlikely that guanethidine or a guanethidine-like drug will largely supplant the ganglionic blocking drugs in the treatment of hypertension.

Bretylium tosylate

Bretylium tosylate is a drug which also selectively blocks sympathetic nervous discharges without blocking parasympathetic nervous discharges.[34] The antihypertensive effect of bretylium tosylate is manifested primarily when the subject is in the orthostatic position, and tolerance frequently develops. The blood pressure is rarely significantly lowered when the subject is recumbent, and the orthostatic effect is usually of little magnitude. The orthostatic hypotensive effect of bretylium tosylate after oral administration lasts approximately 4 to 8 hours.[7,35] The drug therefore is administered three times daily in a dosage range which varies from 300 mg. to over 3,000 mg. daily. Orthostatic hypotensive side effects commonly occur in the morning after the patient arises. The effective dose is frequently unpredictable and unrelated to any hypertensive sign or symptom. The unpredictability of dosage may be related to incomplete absorption of bretylium tosylate from the alimentary canal. Side effects due to the administration of bretylium tosylate include those related to orthostatic hypotension, as well as exertional syncope and constrictive and oppressive chest pain. The chest discomfort may be related to an elevated mean pulmonary arterial pressure.[36] Pain on chewing, epigastric distress, nasal stuffiness, diarrhea, and weakness are additional side effects which have been described. Furthermore, the hypotensive effect of bretylium tosylate is not enhanced by combined treatment with the thiazide diuretics, Rauwolfia serpentina derivatives, or ganglionic blocking agents. For these reasons and especially because of drug tolerance, bretylium tosylate is of little value in the treatment of hypertension.

Ganglionic and adrenergic blocking agents

The ganglionic blocking drugs are powerful and effective antihypertensive agents. With these drugs it is possible to lower the blood pressure in almost all patients who are properly selected.[36] The indications for antihypertensive therapy with ganglionic blocking drugs may include the following: (1) accelerated (malignant) hypertension, (2) hypertensive crisis, and (3) severe hypertension not responsible to other forms of drug therapy. Ganglionic blocking drugs are usually contraindicated in patients who exhibit marked lability of diastolic blood pressure, since it is in this group that profound orthostatic hypotension is prone to occur. Patients with cerebral atherosclerosis, particularly those in the older age group, are not usually considered to be ideal subjects for ganglionic blockade.

The antihypertensive effect of ganglionic blocking drugs may be enhanced by low salt diets, saluretic agents, and other antihypertensive drugs. The dose of a ganglionic blocking agent required to produce a desired antihypertensive effect may be reduced when the drug is used in conjunction with diets low in salt, diuretic agents, or profuse sweating in hot weather, thereby also reducing the undesirable side effects due to the concomitant parasympathetic blockade. The current use of Rauwolfia serpentina derivatives with ganglionic blocking agents also reduces the dose of the ganglionic blocking agent employed and achieves a relatively persistent antihypertensive effect.

It is frequently possible to decrease the dose of the ganglionic blocking drugs by at least 30 per cent with the addition of one of the benzothiadiazine diuretics. Despite the potentiation of the hypotensive effect of the ganglionic blocking drugs by other antihypertensive agents, side effects due to ganglionic (parasympathetic) blockade are frequent and distressing and consequently reduce the usefulness of these drugs. Severe orthostatic hypotension, paralysis of the smooth muscles of the intestine and bladder with resultant constipation and urinary hesitancy, loss of visual accommodation and pupillary dilation, and dryness of the mouth and skin are prominent side effects. The ganglionic blocking agents block the action of acetylcholine which is released from the preganglionic nerve terminal on the ganglionic cell, thereby preventing the transmission

of both sympathetic and parasympathetic autonomic impulses. The parasympathetic blockade may be counteracted by various cholinergic drugs, and the sympathetic blockade may be reversed by adrenergic drugs.

Many of the ganglionic blocking agents are poorly absorbed from the gastrointestinal tract thereby rendering their therapeutic action inconsistent and unpredictable. Mecamylamine is virtually completely absorbed, in contrast to the quaternary compounds, and thereby has a predictability of action not seen with the other ganglionic blocking drugs. Furthermore, the development of drug tolerance to mecamylamine is not so frequent or rapid as with hexamethonium or pentolinium.[illegible] The duration of action of mecamylamine is between 6 and 12 hours or longer. The recommended initial dosage of mecamylamine is 2.5 mg. twice daily with increments of 2.5 mg. daily at intervals of 2 or 3 days until the desired therapeutic effect has been achieved.

The number of patients who require the use of ganglionic blocking drugs to achieve a therapeutic hypotensive effect is decreasing. Because the benzothiadiazine and phthalimidine diuretics and guanethidine are free of the troublesome parasympathetic blockade side effects, they have largely replaced the ganglionic blocking drugs. Thus, the ganglionic blocking agents are used less frequently than previously, and it is to be anticipated that this trend will continue.

Because of the high incidence of side effects, the oral Veratrum alkaloids and adrenergic blocking compounds have limited use in the treatment of hypertension. The Veratrum alkaloids have been relegated to the parenteral route of administration in the treatment of hypertensive emergencies. With the Veratrum alkaloids the reduction in blood pressure is the same when the subject is supine as when he is erect. The Veratrum alkaloids have a pronounced emetic effect and produce bradycardia, and the effective dose required to produce a therapeutic hypotensive effect is close to that which produces emesis.

The adrenergic blocking agents have little clinical usefulness because of the high incidence of side effects and the development of tolerance. Since these drugs produce humoral and neuroeffector blockade, there are no effective antidotes to combat drug-induced hypotension.

Hydralazine

Thirteen years have passed since the pharmacology of hydralazine was first investigated.[illegible] It was found that the hemodynamic effects were characterized by increased cardiac output, decreased peripheral vascular resistance, increased stroke volume, and increased heart rate.[illegible] The renal, coronary, and hepatic circulations exhibit the greatest increases in blood flow.[illegible] The effects of hydralazine on the circulation resemble those produced by pyrogens, and despite intensive study, the mechanism of action is still unclear. Evidence has been published for an adrenergic blocking effect, ganglionic blocking action, central site of action, and dopa decarboxylase inhibition.[illegible]

The initial studies with hydralazine employed large doses which occasionally exceeded 1,000 mg. daily, thereby affording the opportunity to study the chronic toxic side effects. The major side effect on high dosage is a syndrome which resembles systemic lupus erythematosus, with lupus erythematosus cells in the peripheral blood.[illegible] When the dosage is reduced to lower levels or discontinued, the lupus erythematosus-like syndrome disappears, and some patients have resumed treatment with hydralazine without ill effect. Mild arthralgia, skin rash, and conjunctivitis are occasionally seen with doses below 200 mg. daily.

Many controlled studies indicate that, in most patients, hydralazine is an effective antihypertensive agent which has no forbidding side effects if used in reasonable doses. When the dosage is about 300 mg. daily, serious toxicity is not uncommon. Doses of less than 150 mg. daily rarely result in toxic effects, and it is recommended that the dose not exceed 200 mg. daily for any significant length of time. In the dosage range of 50 to 200 mg. daily, hydralazine has a significant antihypertensive effect mainly on the diastolic blood pressure. It is very useful in combination with other antihypertensive drugs which may have a predominant effect on the systolic blood pressure. The starting dose

should not be greater than 25 mg. daily in order to avoid the side effects of headache, dyspnea, and palpitation which are common. Tachycardia due to an associated cardiostimulatory effect which may aggravate coronary insufficiency and be associated with myocardial infarction has been reported. Therefore, hydralazine should be avoided in patients with coronary insufficiency. The dose is usually increased by 25 mg. every second or third day. The increased renal blood flow reported with the administration of hydralazine suggested its preferential use in hypertension associated with renal insufficiency; however, statistics which demonstrate a decreased mortality or morbidity in cases of this nature treated with hydralazine as compared with other antihypertensive agents, have not been published.

Rauwolfia serpentina derivatives

Many preparations of *Rauwolfia serpentina* have been used in the management of patients with hypertension. The crude root powder of the whole root and the alseroxylon fraction are available. The pure alkaloids (reserpine, rescinnamine, and deserpidine) have also been extensively employed. Syrosingopine, a synthetic Rauwolfia alkaloid, was introduced recently.

The Rauwolfia compounds induce hypotension, bradycardia, and sedation.[66-68] This action appears to be mediated by the depletion of norepinephrine and serotonin from the brain and peripheral tissues, with a consequent reduction in sympathetic activity.[69-71]

The hypotensive effect of oral *Rauwolfia serpentina* compounds is mild and requires approximately 3 to 6 days to become manifest. The maximum antihypertensive effect is achieved in 3 to 6 weeks, and after the drug has been withdrawn, hypotensive activity may be observed for as long as 6 weeks. When the *Rauwolfia serpentina* compounds are administered parenterally, the hypotensive effect is observed within 1 to 3 hours and has a duration of approximately 6 to 8 hours. These differences between oral and parenterally administered Rauwolfia are probably related to their rates of absorption. Orthostatic hypotension is occasionally produced by the *Rauwolfia serpentina* compounds and this effect may be potentiated by factors that block sympathetic ganglia or nerves, such as high environmental temperatures, anesthesia, and rest. The antihypertensive effect of Rauwolfia is also enhanced by other drugs.

The bradycardia which is produced by Rauwolfia is useful in the treatment of angina pectoris in hypertensive subjects, and also in the treatment of sinus tachycardia which is frequently associated with hypertension. The sedative effect of *Rauwolfia serpentina* is useful in the management of the apprehensive, tense, and anxious patient. There appears to be little difference in the antihypertensive or side effects of the various *Rauwolfia serpentina* compounds when equivalent dosages are employed. The average daily doses of the crude root, alseroxylon fraction, and reserpine are 200, 4, and .25 mg., respectively. The oral dose of reserpine is occasionally increased to 1 mg. daily. When doses greater than these are employed, there is little increase in the hypotensive effect, and side effects are relatively frequent.

The mild antihypertensive action of these drugs, together with the relatively serious side effects which may be encountered, have diminished the usefulness of the *Rauwolfia serpentina* compounds in recent years. The most distressing side effect is depression, often associated with agitation, occasionally leading to suicide. The symptoms of depression may appear gradually and remain unrecognized for long periods of time. They are reversible and disappear after use of the drug is discontinued. Nasal stuffiness, frequent bowel movements, extensive sedation, weakness, and decreased libido have also been encountered. The availability of more effective antihypertensive agents and the relatively serious side effects of the Rauwolfia compounds have reduced the frequency and indications for their use at the present time. They formerly were indicated either alone or in combination with other antihypertensive drugs, in anxious patients with mild hypertension, especially those with sinus tachycardia or angina pectoris.

Decarboxylase inhibitors

The decarboxylase inhibitors are a group of compounds of particular interest in the

management of hypertension. It has been postulated that the enzyme dopa decarboxylase catalyzes the conversion of dopa to dopamine [illegible] and that an inhibition of dopa decarboxylase activity would decrease the production of norepinephrine. It has recently been found that alpha methyl 3,4-dihydroxy-dl-phenylalanine (alpha methyl dopa), a decarboxylase inhibitor, does inhibit the formation of norepinephrine[illegible] and the finding that alpha methyl dopa results in an increased excretion of 5-hydroxytryptophan and a decreased excretion of 5-hydroxyindole acetic acid when administered to patients with carcinoid tumors is consistent with the decarboxylase inhibition by alpha methyl dopa in man.[illegible]

The biologic activity of alpha methyl dopa resides in the levorotatory isomer and the dextro isomer is devoid of antihypertensive activity in man. It is not known whether the antihypertensive action of alpha-methyl dopa is related to decarboxylase inhibition. The antihypertensive action of this drug is not well correlated with the expected interference with catecholamine metabolism. The delayed onset of the hypotensive response (12 to 24 hours) raises further doubt that the inhibition of catecholamine synthesis is the sole mode of action of alpha-methyl dopa. The mechanism of action of alpha methyl dopa may involve sympathetic blockade at a central or peripheral site. Furthermore, recent evidence indicates that alpha methyl dopa decreases tissue stores of catecholamines. This has been ascribed to the decarboxylation of alpha methyl dopa to produce amine metabolites which have been shown to cause the depletion of catecholamines in various tissues. Alpha methyl dopa results in a reduction of peripheral arterial resistance in the digital circulation of patients with primary hypertension.[illegible]

Many reports have appeared which substantiate the clinical effectiveness of this drug in the treatment of hypertension.[illegible] The average daily oral dose of alpha-methyl dopa is approximately 250 mg. three times daily with a range of 250 to 2,000 mg. The hypotensive effect is manifested in both the supine and erect position, although it is usually more prominent when the subject is in the erect position.

Severe side effects are seldom seen with the administration of alpha-methyl dopa. Sedation has been reported when therapy is first instituted or when the dose is increased. Dryness of the mouth, nausea, vomiting, diarrhea, and edema have also been reported. Occasionally, fever has been observed within the first 2 weeks of administration of alpha-methyl dopa. In a few cases this has been associated with abnormalities in liver function tests, such as in the determinations of transaminase and alkaline phosphatase. No gross clinical evidence of liver damage has ever been reported. The thiazide diuretic drugs potentiate the action of alpha methyl dopa.[illegible] It is not unlikely that as further information on the therapy of hypertension with alpha methyl dopa is published, this drug will find a place in the current antihypertensive armamentarium.

Monoamine oxidase inhibitors

Interest has been stimulated recently in the role of monoamine oxidase (MAO) inhibitors in the treatment of hypertension.[illegible] The introduction of a new drug, pargyline hydrochloride, with profound MAO inhibiting properties has prompted investigations concerning the use and mode of action of MAO inhibitors in the treatment of hypertension.

The mechanism of action of MAO inhibitors is not known. Many papers have appeared with variable conclusions. Diminished responsiveness of the peripheral vascular system to norepinephrine mediated through an increased content of norepinephrine in the blood vessels has been suggested.[illegible] Blockade of the release of norepinephrine at a neuroeffector junction by MAO inhibitors has been proposed.[illegible] It is unlikely that depression of the central sympathetic centers and adrenergic blockade are of major importance.[illegible] Most of the evidence suggests that MAO inhibitors decrease the blood pressure by sympathetic ganglionic blockade.[illegible]

Until recently the MAO inhibitors which have been available possessed only mild or moderate antihypertensive action and had significant side effects. Iproniazid

phenelzine, nialamide, 1-phenyl-2-hydrazinopropane, etc., have fallen into disuse since the introduction of pargyline hydrochloride. Pargyline hydrochloride, which does not have the hydrazine configuration which is thought to predispose to the side effects of optic atrophy, liver toxicity, and visual disturbances, has received significant attention recently in the therapy of hypertension.[illegible] Pargyline hydrochloride has a potency 7 to 10 times that of iproniazid and is an irreversible and powerful inhibitor of MAO in vitro and in vivo. The average therapeutic dose of pargyline hydrochloride is 50 mg. daily, with a range of 25 to 150 mg. a day. Nausea, dizziness upon assuming the erect position, weakness, and diarrhea are side effects which are infrequently seen with the administration of pargyline hydrochloride. In one study the incidence of successful therapeutic results was almost as great in patients with severe hypertension as in patients with mild hypertension.[illegible] Other observers have also obtained favorable results in the treatment of primary hypertension with pargyline hydrochloride.[illegible] A new approach to the treatment of hypertension in man is available with MAO inhibitors. The absence of parasympathetic side effects and the pronounced antianginal and psychic stimulant properties are therapeutic advantages of this group of drugs.

Aldosterone antagonists

The spironolactones or steroidal lactones have also been introduced recently in the treatment of hypertension in man. These compounds possess both diuretic and antihypertensive activity.[illegible] The aldosterone antagonists have been found to have a saluretic and antihypertensive effect when administered to subjects with primary hypertension, even when they are on a diet that is moderately high in salt.[illegible] The saluretic but not the antihypertensive effect is seen in normotensive subjects. The aldosterone antagonists block the action of aldosterone and other mineralocorticoids. Their mode of action on the blood pressure is similar to that of the thiazide diuretics. Neither a reduction in total body sodium nor in plasma volume is primarily responsible for the antihypertensive action of these compounds. The antihypertensive effect of the aldosterone antagonists is maintained even when the plasma volume is re-expanded to the value previously present before the drug was administered. Studies on sodium balance indicate also that the antihypertensive effect is unrelated to a loss of total body sodium.

Hypertensive subjects who respond to the thiazide diuretics usually respond to the aldosterone antagonists. Furthermore, the antihypertensive effect of the aldosterone antagonists is enhanced by the concomitant administration of the thiazide diuretics.

The average daily dose of spironolactone is 100 to 300 mg., depending on the pharmaceutical compounding of the preparation employed. Initially the serum potassium may rise and later decline to control levels. There is usually no effect on the serum uric acid. The side effects due to the administration of aldosterone antagonists are usually infrequent and mild. Drowsiness and skin rash have been reported. It is likely that this group of compounds will play an increasing role in the treatment of human hypertension.

Hypertensive emergencies

The hypertensive emergencies are situations in which the elevation of blood pressure presents an immediate threat to the patient's life, and include hypertensive crises, hypertensive encephalopathy, acute *secondary hypertension, and acute hypertension* associated with toxemia of pregnancy or with cerebral hemorrhage. Many of the signs and symptoms of the hypertensive emergencies are related to decreased cerebral blood flow secondary to increased cerebral vascular resistance and cerebral edema.[illegible]

Although many drugs have been used in the treatment of acute hypertensive emergencies in the past, only a few drugs are commonly used at the present time. The therapeutic effectiveness, predictability of action, and relative freedom from side effects of trimethaphan camphorsulfonate, a short-acting ganglionic blocking agent which also may have a direct peripheral vasodilator effect, make this agent of particular value for the production of controlled hypotension. Trimethaphan cam

phorsulfonate is administered intravenously by diluting one ampule (10 ml., 5 mg./ml.) to 500 ml. and adjusting the rate of administration to the requirements of the situation. The average intravenous dose is 3 to 4 mg. per minute. Frequent determinations of blood pressure are required in order to maintain proper control and the hypotension produced by trimethaphan camphorsulfonate may be reversed by the intravenous administration of pressor agents, such as norepinephrine or angiotensin II. The antihypertensive effect of trimethaphan camphorsulfonate is achieved almost immediately and when administration of the drug is stopped the blood pressure rises again within several minutes.

Several other ganglionic blocking agents with a more prolonged duration of action than trimethaphan camphorsulfonate are also available for parenteral use in hypertensive emergencies. Pentolinium may be administered intramuscularly; an initial dose of 2.5 mg. is followed at 30-minute intervals by subsequent doses which vary between 2.5 and 50 mg., depending upon the blood pressure response. Doses greater than 50 mg. rarely produce any additional hypotensive response. The frequency of administration is determined by the desired therapeutic effect. Severe side effects due to parasympathetic ganglionic blockade are frequent, particularly with larger doses. Both pentolinium and hexamethonium may be administered intravenously at a concentration of approximately 0.1 mg. per milliliter at a rate adjusted to maintain the desired antihypertensive effect. Elevation of the head of the bed enhances the hypotension. When one wishes to reduce the amount of fluid administered, pentolinium may be given intravenously in a concentrated solution of 10 mg. in 1 to 10 ml. of fluid. The prominent parasympathetic side effects associated with the administration of pentolinium and hexamethonium and the prolonged duration of their effect have reduced the frequency of their use.

Parenteral reserpine has been used extensively in the treatment of hypertensive emergencies. However, the relatively long latent period of 1 to 2 hours before the blood pressure decreases after intramuscular or intravenous administration, the relatively unpredictable hypotensive response, and the cerebral depression which is frequently observed are undesirable effects which have restricted the use of this agent. Reserpine is administered parenterally, initially in a dose of 0.5 to 2.5 mg. If the antihypertensive response to this dose is not adequate, then an additional 2.5 mg. is administered approximately 3 hours later. Individual doses may be increased to as much as 10 mg., although there is rarely any additional hypotensive effect with doses greater than 5 mg. After the desired degree of hypotension has been obtained, maintenance therapy employing parenteral reserpine usually requires administration every 8 to 12 hours. Although the maximum antihypertensive effect of parenteral reserpine is usually obtained in 3 hours, the tranquilizing effect of this drug may be observed in approximately 45 minutes. Any of the commonly available vasopressor agents may be used to reverse excessive hypotension.

Parenteral Veratrum drugs are potent antihypertensive agents which are usually associated with nausea, vomiting and difficulty in stabilizing levels of blood pressure. Their antihypertensive effect is manifested in both the erect and supine positions. The onset of action is usually within several minutes. These drugs are usually given intravenously with an initial priming dose followed by a maintenance dose. The priming dose of alkavervir is 0.5 μg per kilogram of body weight per minute over a 20-minute period. When the desired antihypertensive effect is achieved, the maintenance dose is substituted and usually consists of 4 mg. of alkavervir in 1,000 c.c. of fluid administered at a rate necessary to maintain the desired level of blood pressure. Protoveratine may be used in a similar fashion. The priming dose is 0.1 mg. in 10 ml. of fluid administered at a rate of 0.5 ml. per minute. The maintenance dose of protoveratine is 2 mg. diluted in 1,000 ml. of fluid. After the immediate hypertensive emergency is over, these drugs may be administered intramuscularly. The alkavervir may be administered in a dose of 0.6 mg. every 4 to 6 hours with an increase in the dose by 0.2 mg.

with each injection until the desired therapeutic effect is achieved The protoveratine may be administered intramuscularly at an initial dose of 0 6 ml (0 12 mg) followed by subsequent doses which are increased by 0 2 ml every 4 to 6 hours until the desired therapeutic effect is achieved The nausea vomiting and bradycardia associated with the Veratrum drugs have reduced the therapeutic usefulness of these preparations.

The choice of drug or drugs to be used in the treatment of the hypertensive emergencies depends on the selection of an agent that will achieve the desired antihypertensive effect rapidly without creating undesirable side effects or difficulty in controlling the blood pressure The same general principles which guide the physician in the use of the oral antihypertensive drugs should also be applied when antihypertensive agents are administered parenterally Trimethaphan camphorsulfonate would appear to have the greatest combination of desirable effects and will undoubtedly be used with increasing frequency

Concluding remarks

It is clear that great strides have been made recently in the treatment of hypertension It is also undoubtedly true that much of what has been written here will be revised in the near future. This is a source of great satisfaction since it indicates that the prodigious efforts of innumerable clinics and investigators throughout the world are continuously productive and have diminished and will continue to reduce the mortality and morbidity of hypertensive disease

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

The treatment of endocarditis

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The constant increase in the number of antimicrobial agents available, the changing etiological patterns, and the altered antibiotic susceptibilities of certain microorganisms necessitate a periodic review of the therapeutic regimens for endocarditis. The following summary is derived from the author's experience and interpretation of the literature.

1. Streptococcus viridans. This microorganism remains the most frequent cause of bacterial endocarditis. Almost all strains are sensitive to penicillin. Occasionally, however, cases due to alpha hemolytic streptococci which are resistant to over 0.5 units per milliliter of penicillin have been reported, and it is imperative therefore to determine the in vitro antibiotic susceptibility pattern of each strain.

It is generally agreed that a minimum therapeutic regimen consists of 14 days of treatment with at least 2,400,000 units of penicillin G daily, together with 1.0 to 1.5 Gm. of streptomycin. Along with many investigators, we believe that the relapse rate is higher with short term treatment, and therefore administer penicillin for 28 days. There is no unanimity of opinion about the type of penicillin. We give 1,200,000 units of procaine penicillin intramuscularly every 4 to 6 hours. Others feel strongly that injections of aqueous penicillin G should supplement or replace procaine preparations, arguing that briefly sustained high concentrations of the antibiotic are more effective than longer sustained lower levels. Bacteriologic cure has been so regularly achieved in alpha streptococcal endocarditis treated with either procaine or aqueous penicillin that neither preparation would appear to show clear superiority. If the 28-day regimen is chosen for infections due to penicillin-sensitive strains, the use of streptomycin is optional.

Many reports indicate that oral phenoxymethyl penicillin or phenethicillin, 500 mg. every 4 to 6 hours, can be substituted for parenteral preparations. Unfortunately, absorption is not entirely predictable. If a laboratory is available which can measure the level of antibiotic in the blood, oral therapy is satisfactory; otherwise, because of the potential dangers of failure to achieve bacteriologic sterilization, penicillin should be administered parenterally.

If a strain is resistant to penicillin in vitro, the antibiotic should be given intravenously in a dosage of 10,000,000 to 40,000,000 units daily for 4 to 6 weeks, accompanied by streptomycin, 1.0 to 1.5 Gm. a day for 2 to 3 weeks.

Even if a patient is allergic to penicillin, he should be treated with penicillin if possible. The great majority of patients can be "desensitized" by the administration of 0.01 unit of penicillin intradermally, followed every 1 to 2 hours by tenfold increments in dosage given subcutaneously. If 100,000 units are tolerated without incident, an intravenous infusion should be started and penicillin given by this route for the duration of therapy. It should be

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emphasized that even after successful desensitization there may be allergic reactions including anaphylactic shock and laryngeal edema. Fortunately such reactions occur infrequently. Should allergic reactions occur, it may still be possible to use penicillin by giving the antibiotic and adrenal glucocorticoids concurrently.

Bacteriostatic antibiotics including erythromycin, the tetracyclines, and chloramphenicol eradicate the infection in no more than one third of the cases and are not recommended, nor are the newer semisynthetic penicillins such as oxacillin and methicillin which are less effective than penicillin G.

Staphylococcus. Endocarditis due to both coagulase-positive and coagulase-negative staphylococci has increased in recent years. Penicillin in dosage of 6,000,000 to 10,000,000 units daily for 4 to 6 weeks remains the treatment of choice for penicillin-sensitive strains (susceptible to less than 1 unit per milliliter).

If the staphylococcus is penicillin resistant, methicillin 6 to 12 Gm. daily, or parenteral oxacillin are the antibiotics of choice since virtually all strains are susceptible to these agents. The latter, which is given in a dosage of 3 to 6 Gm. daily for at least 4 weeks, is perhaps the most potent antistaphylococcal agent currently available. Oxacillin can also be given by mouth but as with other penicillin preparations, absorption varies from patient to patient. Consequently, parenteral oxacillin is recommended for severe or overwhelming staphylococcal infections, with the change to oral therapy being made only after a minimum of 2 weeks. Since methicillin has occasionally produced bone marrow depression and agranulocytosis, constant hematological surveillance is necessary. The administration of oxacillin has not yet been associated with hematological abnormalities.

Vancomycin in a dosage of 2 or 3 Gm. daily intravenously is also an effective agent. Approximately 70 per cent of the patients with severe staphylococcal infections recover after its administration. The dosage must be kept to a maximum of 1.5 Gm. daily in azotemic patients since renal failure interferes with the excretion of vancomycin, thus causing high concentrations in the blood which are followed by deafness in a considerable number of patients. Vancomycin rarely produces renal damage in patients with normal kidneys, but when these organs are diseased, azotemia may appear or increase during its administration.

Kanamycin is effective in vitro against most penicillin-resistant staphylococci, but auditory and renal toxicity occur frequently and it should be used only if methicillin, oxacillin, and vancomycin have failed. Bacitracin is equally effective but even more toxic to the adult kidney.

Bacteriostatic agents, including erythromycin, novobiocin, the tetracyclines, and chloramphenicol, have been recommended by some, but data which support their use are not convincing. In contrast, there is considerable evidence that, whereas bactericidal agents are effective against staphylococcal endocarditis, bacteriostatic agents are not. Without convincing data that bacteriostatic agents are effective, they cannot be recommended unless bactericidal antibiotics have failed.

Penicillin, even in very large dosage, is not recommended in the treatment of endocarditis due to penicillin-resistant staphylococci.

3. Enterococcus. The evidence is overwhelming that penicillin in combination with streptomycin is the regimen of choice in enterococcal endocarditis. Aqueous penicillin should be given in a dosage of 20,000,000 units daily for 6 weeks, and 1.5 Gm. daily of streptomycin should accompany it for 21 to 28 days. Some investigators believe that procaine penicillin, 6,000,000 units daily, together with probenecid can be substituted for aqueous preparations, but most consider this regimen to be inadequate. It should be emphasized that enterococci are ordinarily resistant to either penicillin or streptomycin alone in vitro, but that these two agents act synergistically against enterococci both in vitro and in vivo. Large amounts of penicillin given alone, even over a prolonged period, *will not* effect a cure in most patients with enterococcal infections.

No other agent is reliable in the treatment of enterococcal endocarditis. Ristocetin has been effective in some cases and if penicillin and streptomycin fail, should be tried in a dosage of 3 to 6 Gm. daily

parenterally for 14 to 21 days. Hematological toxicity occurred with early ristocetin preparations but is much less now with improvement in manufacture

If the infection persists or recurs, focal splenic or intra-abdominal abscesses should be sought If no abscesses are detected and if there is failure to achieve bacteriologic cure with penicillin plus streptomycin or with ristocetin the patient should be re treated with penicillin and streptomycin for 6 weeks (streptomycin for 3 or 4 weeks) the penicillin should be given intra venously in a dosage of 50 000 000 to 100 000 000 units daily with probenecid

4 Candida Endocarditis due to species of Candida has become more common as a consequence of intensive antibiotic treat ment increased use of intravenous infusions and bolder cardiac surgery The only agent currently available for therapy is amphotericin B Although amphotericin appears to be effective in acute Candida fungemia with or without involvement of previously normal valves, it usually fails in subacute endocarditis—only a few recoveries have been reported The vegetations are characteristically large and their surgical removal may be a helpful adjunct to amphotericin

Amphotericin which is given intravenously in a dosage of 30 to 60 mg daily (or every other day) for 4 to 12 weeks, is an extremely toxic agent which causes chills, fever vomiting phlebitis, azotemia hypokalemia, thrombocytopenia anemia, leukopenia, non-thrombocytopenic purpura and hepatic necrosis. Therefore it should not be given unless there is convincing evidence of severe systemic mycotic infection

Nystatin given orally is not absorbed and cannot be used in the treatment of systemic infections. Parenteral nystatin preparations were found to be exceedingly toxic and are no longer available

5 Bacteroides Treatment should be based on in vitro sensitivity tests but in general tetracycline or chloramphenicol plus streptomycin given for 4 to 6 weeks is the treatment of choice As with enterococcal infections if treatment fails focal drainable abscesses should be sought.

6 Gram negative enteric bacteria Endocarditis due to *Escherichia coli Aerobacter aerogenes* and species of Proteus, Paracolobactrum and Pseudomonas is increasing Treatment is usually difficult and the antibiotic regimen is virtually completely dependent on in vitro sensitivity tests. If the patient is acutely ill and these tests have not yet been completed kanamycin and chloramphenicol are a reasonable combination since most of the infections are hospital acquired and the microorganisms are resistant to tetracycline and streptomycin In Pseudomonas infections, colistin methanesulfonate is usually the most effective agent and has far less renal and nervous-system toxicity than does kanamycin. If the etiological agent is *Proteus mirabilis* penicillin in large dosage perhaps together with kanamycin is the regimen of choice.

If these infections arise postoperatively surgical removal of vegetations and or infected ligatures may be valuable at times a necessary adjunct to antibiotics.

7 Streptobacillus moniliformis Penicillin is effective against virtually all strains and is the drug of choice It is given in the same dosage and for the same duration as for *Streptococcus viridans* infections.

8 Miscellaneous A variety of commonly isolated organisms such as diphtheroids, can occasionally produce endocarditis, as can less frequently isolated microbes, such as strains of Nocardia or Actinobacillus. Even bacterial "L" forms have been incriminated as the causative agents in endocarditis. The antibiotic regimen chosen depends on in vitro results.

This category appears likely to increase with improvement in culture techniques and with an increase in the number of individuals who are inordinately susceptible because of successful antimicrobial and antimetabolite treatment of severe underlying disease It is also probable that many of the "L" forms and unusual microorganisms will resist even the most vigorous antibiotic treatment

Contractile tension in the myocardium*

It is regrettable that some authors refer to the pressure in a cavity as the tension. Pressure in a hollow organ or tubular structure is the force acting radially against the wall per unit surface area whereas tension is the tangential force in the wall of the organ. The tension developed by the contracting myocardium has received renewed interest on account of the concept that it is one of the major determinants of the oxygen consumption of the blood perfused beating heart.[1-3] This tension may be referred to as the *contractile* tension (or stress) and is a characteristic property of living muscle tissue. It has no counterpart in inanimate matter. The assumption has been that the laws which apply to nonliving elastic bodies also apply to the living heart muscle undergoing contraction. Unfortunately there has been no uniformity in expressing contractile tension in the myocardium.

Until very recently there was no direct method for measuring myocardial tension. Recourse was had to calculating it in accordance with the law of Laplace which applies to a distensible membrane that has a spherical or cylindrical shape. In a distended, perfectly spherical elastic membrane, if P represents the transmural pressure across the wall of the membrane and r the radius, the total force at the equatorial circumference that tends to separate the two hemispheres can be shown mathematically to be equal to the product of P and the area of the circle at the equator or $P \times \pi r^2$. Some authors[4] have applied this to the left ventricle on the assumption that the cavity is spherical. "Tension" has been calculated by the formula,

$$T = P \times \pi r^2 \qquad (1)$$

According to this definition, T represents the *force across the total cross-sectional area of the muscle at the* equator (Fig. 1). Levine and Wegman have calculated myocardial tension, defined in this way, at the beginning and at the end of the ejection period, from the pressures prevailing at these moments and the calculated internal radii from the end-diastolic and end-systolic ventricular volumes. It should be noted that, in hearts of different anatomic size, myocardial tension calculated in this way would depend not only on the curvature of the wall but also on the circumferential length (r^2). To overcome this difficulty, tension (T) has been more appropriately defined as the *force per unit length of circumference* at the equator. With this definition of tension the foregoing relationship may be written as follows

$$T \times 2\pi r = P \times \pi r^2$$

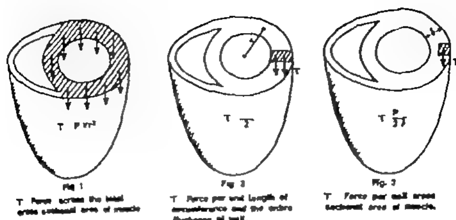
$$T = \frac{Pr}{2} \qquad (2)$$

This is the familiar equation for calculating surface tension in liquid drops (for soap bubbles $T = \frac{Pr}{4}$ since there are two surfaces of air-liquid).

Equation 2 is the more generally used Laplace formula for calculation of the contractile tension in the wall of the left ventricle.[6-8] It represents the tangential force per unit length of circumference by the *entire thickness* of the muscle wall (Fig. 2). With regard to the applicability of Equation 2 to thick-walled structures, the reader is referred to Burton's discussion in the *Handbook of Physiology*.[9]

If the mean tension for the whole period of contraction and relaxation is to be calculated, P should be the integrated mean left ventricular pressure during these periods, and r should be the integrated radius. Also, r should be the average of internal (endocardial) and external (epicardial) integrated radii. Unfortunately, accurate measurements of these parameters have not been possible under experimental conditions. Holt has calculated the *end-systolic* tension per unit length of circumference in the left ventricle of dogs, using the peak systolic ventricular pressure and the internal radius at the end of ejection calculated from the end-systolic blood volume ($ESV = 4/3\pi r^3$). Rodbard[10] has used the mean systemic arterial pressure to calculate the mean left ventricular tension per unit length of circumference. However, he has used the internal radius of the left ventricle at the *beginning* of ejection by calculating it from the stroke volume on the assumption that the ventricle has a negligible residual volume at the end of ejection. For the heart of the closed-chest dog or of man this assumption would not be justified,[11] but may be justified in Rodbard's open-chest experiments, since Rushmer and his associates[12] have shown that thoracotomy reduces considerably the size of the dog heart. Whether or not the residual volume is negligible in open-chest dogs or in the denervated heart of the heart lung preparation has not been investigated by the recently developed methods. The calculations of Holt and Rodbard[10] give the tension developed across a unit length of circumference by the entire thickness of the left ventricular wall. Since heart

*Thanks are due to *Professor Salim Nassar* of the Physics Department, American University of Beirut, for critically reviewing the manuscript.



Figs. 1-3. Various definitions of contractile tension in the myocardium and the formulas used to calculate each.

of different anatomic size having different wall thicknesses (h), it would be better to express tension (T) per unit circumferential length and unit thickness of wall. In other words, express tension as the *force per unit cross-sectional area* of heart muscle (Fig. 3). The value of this consideration has been pointed out by Burton and Badeer.[1,2] The Laplace formula would then be written as follows:

$$T = \frac{P}{2h} \qquad (3)$$

Linzbach[20] has calculated myocardial tension at the beginning and toward the end of ejection, in accordance with this definition. When r is expressed in centimeters, P in dynes per square centimeter, and h in centimeters, T will be in dynes per square centimeter. Since the law of Laplace may be applied to hearts of widely varying size in the same and different species, it is recommended that all future calculations of myocardial tension be expressed in terms of force per unit cross-sectional area (Equation 3). If the mean tension during the cardiac cycle is to be calculated, one should determine the integrated mean intraventricular pressure, the stroke volume, the end-systolic volume, and the ventricular wall thickness. The last parameter may be measured approximately after the animal has been sacrificed. From these data, one can calculate the internal and external radii and their approximate mean value during ejection, assuming that the rate of change of radius is constant.

Despite all these precautions, the accuracy of such calculations will still be somewhat limited by the following factors: (1) Radial pressure in various layers of the myocardium is probably not the same and equal to the intraventricular pressure. (2) The ventricular cavity is not spherical, so that tension will not be the same in different regions of the myocardium. (3) Shortening of cardiac muscle fibers per se causes a sharp fall in tension, as was demonstrated by Lundin.[21] This would play a role in reducing myocardial tension during the ejection phase of systole, apart from the influence of the decrease in ventricular radius (law of Laplace).

It should be pointed out that the myocardial tension calculated by the foregoing formulas is in no way identical to the force or tension of the myocardium as recorded by the strain gauge arch of Walton.[22,23] Recently a force gauge has been designed and used on dogs to measure the tension across a slit made in the wall of the left ventricle. Unfortunately, in this procedure the cross-sectional area of the tissue whose contractile force was recorded was unknown and variable, and it would be impossible to compare quantitatively the data obtained from different experiments. Nevertheless, the study demonstrated that Equation 1 holds true for the left ventricle, and that the myocardial tension declines soon after the beginning of the ejection of blood from the left ventricle, confirming a prediction made by several investigators on the basis of the law of Laplace.[4,20]

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Annotations

Contractile tension in the myocardium*

It is regrettable that some authors refer to the pressure in a cavity as the tension. Pressure in a hollow organ or tubular structure is the force acting radially against the wall per unit surface area, whereas tension is the tangential force in the wall of the organ. The tension developed by the contracting myocardium has received renewed interest on account of the concept that it is one of the major determinants of the oxygen consumption of the blood-perfused beating heart. This tension may be referred to as the *contractile* tension (or stress) and is a characteristic property of living muscle tissue. It has no counterpart in inanimate matter. The assumption has been that the laws which apply to nonliving elastic bodies also apply to the living heart muscle undergoing contraction. Unfortunately there has been no uniformity in expressing contractile tension in the myocardium.

Until very recently there was no direct method for measuring myocardial tension. Recourse was had to calculating it in accordance with the law of Laplace which applies to a distensible membrane that has a spherical or cylindrical shape. In a distended, perfectly spherical elastic membrane, if P represents the transmural pressure across the wall of the membrane and r the radius, the total force at the equatorial circumference that tends to separate the two hemispheres can be shown mathematically to be equal to the product of P and the area of the circle at the equator or $P \cdot \pi r^2$. Some authors[1] have applied this to the left ventricle on the assumption that the cavity is spherical. Tension has been calculated by the formula

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t has produced death. However it appears likely that the mechanism of death in crucifixion was suffocation. The chain of events which ultimately led to suffocation are as follows. With the weight of the body being supported by the sedulum, the arms were pulled upward. This caused the intercostal and pectoral muscles to be stretched. Furthermore movement of these muscles was opposed by the weight of the body. With the muscles of respiration thus stretched the respiratory bellows became relatively fixed. As dyspnea developed and pain in the wrists and arms increased, the victim was forced to raise the body off the sedulum, thereby transferring the weight of the body to the feet. Respiration became easier but with the weight of the body being exerted upon the feet, pain in the feet and legs mounted. When the pain became unbearable, the victim again slumped down on the sedulum, with the weight of the body pulling on the wrists and again stretching the intercostal muscles. Thus, the victim alternated between lifting his body off the sedulum in order to breathe and slumping down on the sedulum to relieve the pain in his feet. Eventually he became exhausted or lapsed into unconsciousness so that he could no longer lift his body off the sedulum. In this position, with the respiratory muscles essentially paralyzed, the victim suffocated and died.

If death came too slowly and public interest waned, as it usually did after several hours, the victim's legs were broken below the knees so that he could no longer lift his body off the sedulum. This practice, called the *crurifragium*, was swiftly followed by suffocation and death.

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Fibrillatory wave size as a clue to etiological diagnosis

Fibrillatory wave size may be related in most instances to etiological diagnosis. Recently Thurmann and Janney reported a method for classifying fibrillatory wave size and relating this to the presence of arteriosclerotic heart disease and rheumatic heart disease.

We have reviewed all electrocardiograms with atrial fibrillation made at the Medical College Hospital from January, 1956, to June, 1962, and from the private practice of one of us (P.C.G.), without previous knowledge of the clinical diagnoses. The tracings were classified according to the amplitude of the f waves in Lead V₁ measured from the trough to the peak (Fig. 1). The f waves were considered as *fine* when the amplitude measured 0.5 mm. or less and *coarse* when the amplitude exceeded 0.5 mm. The tracings were further classified as *straight-line fibrillation* when the f waves were indistinguishable from the base line, and *very coarse* when the amplitude exceeded 2.5 mm. Hospital charts were reviewed for clinical diagnosis and for the duration of atrial fibrillation with or without congestive heart failure. Also an attempt was made to correlate f wave size with the presence of left atrial enlargement when noted at autopsy, cardiac fluoroscopy, or cardiac surgery.

A total of 340 cases of atrial fibrillation were studied. The ages of the patients ranged from 6 to 92 years. There were 160 patients with arteriosclerotic heart disease, 92 with rheumatic heart disease (89 had mitral stenosis and/or mitral insufficiency with or without aortic valve disease, and 3 had aortic stenosis and insufficiency), 12 with thyrotoxicosis, 30 with functional atrial fibrillation, 20 with hypertensive cardiovascular disease, 17 with combinations of diseases, and 9 with disease entities not classified in the study.

The incidence of each f wave character in the various diagnostic categories was determined. Coarse f waves predominated in rheumatic heart disease (74 per cent), thyrotoxicosis (59 per cent), and functional atrial fibrillation (70 per cent). Only 14 per cent occurred in arteriosclerotic heart disease, and 5 per cent in hypertensive heart disease. Fine f waves predominated in arteriosclerotic heart disease (71 per cent) and hypertensive heart disease (50 per cent). They were also found in rheumatic heart disease (13 per cent), functional atrial fibrillation (30 per cent), and in thyrotoxicosis (33 per cent). When two disease entities occurred, f waves were fine if arteriosclerotic heart disease was present, and coarse if rheumatic heart disease existed. When arteriosclerotic heart disease and rheumatic heart disease occurred concomitantly, coarse f waves predominated. Straight-line fibrillation occurred only in patients with arteriosclerotic (15 per cent) and hypertensive heart disease (45 per cent). Very coarse f waves occurred only in rheumatic heart disease (13 per cent) and in 1 patient with thyrotoxicosis (8 per cent).

X-ray, autopsy, and operative findings revealed close relationship between coarse f waves and left atrial enlargement in patients with rheumatic heart disease. The fact that patients with thyrotoxicosis and with functional atrial fibrillation had coarse f waves without left atrial enlargement suggest that there may be factors other than left atrial size. Right atrial size and the ratio of hypertrophy and

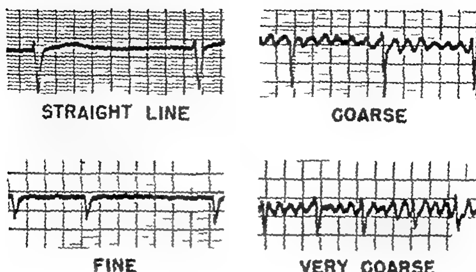


Fig. 1. T pes of fibrillatory es n Lead V

dilatation of the tria are probably other important factors. Prinzmetal th the aid of high-speed cinemat graphs nd direct trial lead made direct observ tions on the fibrillating tria of patients undergoing cardiac surgery. Heterorh thmic large contraction wa es t irregular rate were noted, and corresponding irregular trial electrocardiographic complexes at the same rat presumed t correspond to the f es seen in the elect ocardiogram during trial fibrillation. Different rates and configura ion ere found in the two tria. There p peared to be no relationship between f e char acter and the duration of the trial fibrillation ith or without congestiv heart failure.

I summary, coarse f av es occurred primarily in rheumatic heart disease thyrotoxicosis and func tional trial fibrillation. Fine f w es ppeared primaril in arteriosclerotic and hypertensi heart disease. Straight-line fibrillation as seen onl in the latter t categories, hereas er coarse f w es occurred only in rheumatic heart disease nd thyrotoxicosis.

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Portable chest roentgenography and its value in acute myocardial infarction

It is clinical maxim that no physical examination is complet without a chest roentgenogram. Nevertheless chest roentgenography is frequently ignored as routine procedure nd especiall in patients who are considered t be too ill t be transported t the department of radiology. There is little or no excuse for such neglect in the former instance and in the latter lack of ppreciation of the utility of portable chest roentgenography. Indeed, chest roentgenogram can be obtained t the patient bedside and little if any effort is required of the patient undergoing portable chest roentgenography. The upper part of the bed is elev ted so that the patient is in the sitting position nless the patient is unconscious nd necessarily supine. A casset is slipped behind the patient back, nd exposure is made t a target-to-film distance of 48 inches.

I ha employed portable chest roentgenography routine measure for long time in all patients admitted t my service t Episcopal Hospital. Ben con entional study as considered t be contra indicated nd has yet to encounter y adverse effect. The chest roentgenogram so obtained is technically satisfactory ithout blurring, and,

frequently differentiation from one obtained in the conventional manner is difficult. Its value has been inestimable in the detection and recognition of cardiopulmonary diseases. The patient may be confined to bed because of a stroke or circulatory failure with negative or nonspecific clinical cardiopulmonary findings. Yet, the portable chest roentgenogram may uncover a neoplasm, pneumonia or fluid. Moreover there may be changes in the size and shape of the cardiac silhouette which provide clues that are helpful in diagnosis, prognosis, and treatment.

The portable chest roentgenogram has also been used routinely in patients confined to bed because of the clinical suspicion of acute myocardial infarction. Usually these patients were reported to show no abnormality. The cardiac silhouette was not enlarged, and the lung parenchyma was normal. Nevertheless, Dr. Joseph Nussbaum, associate radiologist at Episcopal Hospital, was intrigued by the finding of bulging of the right lateral border of the cardiac silhouette. Although this finding was impressive, I was and remain reluctant to ascribe pathologic meaning to it alone, for several reasons. First, this bulging is difficult to measure precisely and recognition of it at present depends entirely upon inspection and awareness of the normal. Second, although the normal right atrial border is characterized by a gentle outward curvature, exceptions are common, and particularly when the diaphragm is elevated, as obtains when a roentgenogram is taken in other than the standard position. Third, many conditions other than acute myocardial infarction are associated with bulging right atrial border. Nevertheless, increased outward curvature of the right lateral border of the cardiac silhouette is a common finding in acute myocardial infarction.

Being unhappy with this finding alone for the recognition of an acute myocardial infarction, I continued to search for additional signs. As a result of my own interest[2] and the reports by others of the pulmonary venous pattern in left ventricular failure,[3-5] I examined carefully the venous markings in the portable chest roentgenogram, with the specific purpose of recognizing any distinguishing features of acute myocardial infarction.

In normal persons the pulmonary venous markings to the upper lobes are not prominent. They are best detected in the left upper lobe because of the absence of contiguous density and are recognized as pulmonary venous markings by their solid linear character and their somewhat oblique direction to the left upper lobe from the lower portion of the left hilum. Moreover normally the pulmonary venous markings in the upper lobes are less numerous and smaller than those in the right lower lobe. The vascular markings in the left lower lobe are frequently obscured by the cardiac silhouette. This normal venous pattern is reversed in persons with left ventricular failure the veins to the upper lobes are prominent and indeed larger than those in the lower lobe. In fact the actual caliber of the pulmonary vascular marking in the lower lobe appears to be considerably reduced.

In a series of 20 consecutive patients admitted to the hospital because of chest pain which aroused suspicion of an acute myocardial infarction, a normal venous pattern was found in 10, and in only one of these was an acute myocardial infarction demonstrated subsequently. Reversal of the normal venous pattern was found in the other 10 and of these, 9 had an acute myocardial infarction. The tenth one had coronary artery disease and subclinical left ventricular failure which had been precipitated by an acute respiratory infection. Concerned with the possibility of artefactual production of this pattern because of position and projection, Dr. Nussbaum and I satisfied ourselves of its absence by comparison of roentgenograms taken in various positions and projections, so long as the roentgen tube was not situated inferior to the center of the chest.

The findings of bulging of the right lateral border of the cardiac silhouette and reversal of the normal pulmonary venous pattern imply the occurrence in acute myocardial infarction of left ventricular failure which is frequently not otherwise detectable. Because of impaired contractility of the left ventricle, an increase in filling pressures occurs.

Absence of these roentgenographic findings does not necessarily exclude an acute myocardial infarction, presumably because the resultant hemodynamic abnormality is insufficient to produce detectable roentgenographic change. Conversely their presence does not necessarily indicate acute myocardial infarction, for any condition which compromises left ventricular function may be manifested similarly. It is important, therefore, to interpret the significance of these findings with knowledge of the clinical situation.

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Book reviews

PERIPHERAL CIRCULATION IN MAN (British Medical Bulletin May 1963 Volume 19 Number 2).

This issue of the *British Medical Bulletin* should interest all who are engaged in study of the peripheral circulation. The issue consists of twelve papers and an introduction by Professor Henry Barcroft. The authors are British. They are experts who using well known methods, have been engaged in study of the circulation of man. All of the methods used have shortcomings some of which are much greater than others. The difficulties are discussed in some instances, e.g. by David Greenfield and associates in a presentation entitled "Investigation of Peripheral Blood Flow," whereas other authors accept their methods without expressing reservations. Unfortunately the papers are extremely brief so that critique of methodology probably could not be included in the presentations. Nevertheless, the seasoned investigator will observe opinions and concepts entertained by the respective authors. The beginner will find it easy to become oriented in selected aspects of the problems encountered in the study of the peripheral circulation of man.

The titles of the papers contained in this issue are "Nervous Control of Cutaneous Circulation," "Circulation in Skeletal Muscle," "Autonomic Transmitter Mechanism," "Adrenaline and Limb Blood Vessels," "Noradrenaline, Isoprenaline, Noradrenaline and Dopamine," "Hyperaemia Induced by Exercise and Ischaemia," "Local Effects of Temperature," "Venous Tone," "Critical Closure in Human Limbs," "Capillary Filtration," "Clinical Implications," "Investigation of Peripheral Blood Flow."

This is a good issue of the *British Medical Bulletin*. It is recommended not only to medical students, physiologists and those interested in investigative studies of the peripheral circulation but also to clinicians who wish to know more about the regulation of the peripheral circulation.

The *British Medical Bulletin* is an excellent publication which devotes its respective issues to important problems in medicine. This issue is an example.

YEARBOOK OF CARDIOVASCULAR AND RENAL DISEASES, 1961-1962 SERIES. Edited by W. Proctor Harvey, John W. Kirklin, Alexander S. Nadas, Oglesby Paul, Victor E. Pollak, T. Joseph Reeves, Robert W. Wilkins, Irving S. Wright. Chicago 1963 Yearbook Medical Publishers. 474 pages. Price $10.

This is the newest edition of the Yearbook Series. A notable array of authors has covered the recent papers in cardiovascular and renal diseases and made a comprehensive review as completely as could be done in this compact-sized book. The abstracts are well written and a number of illustrations from many papers are reproduced. Naturally some of the more complex articles are occasionally too terse to be of great value, providing no more than a superficial acquaintance. However they do serve to pinpoint the high spots in two fields in the foreign and American literature. The editors have added considerably by their own candid comments on many papers. The practicing internist as well as the house officer will find this book of value but obviously it will not take the place of reading the contemporary journals.

The print and paper are of high quality.

The modest price will make this an attractive addition to the library of the physicians interested in these fields.

Announcements

An advanced seminar in the DIAGNOSIS OF CARDIAC ARRHYTHMIAS, with emphasis on both clinical and electrocardiographic features will be held at the Tampa General Hospital, Tampa, Fla., Nov. 1-4, 1963.

The faculty will include Dr. Harold H. Bix, Baltimore; Dr. James L. Gouaux, St. Petersburg; Dr. Albert M. Klein, Beckley; and Dr. Ralph Miller, Newark. The seminar will be under the direction of Dr. H. J. L. Marriott, Director of the Cardiology Center, Tampa General Hospital.

Registration is limited to 50. For further details write to the Cardiology Center, Tampa General Hospital, Tampa 6, Fla.

A YOUNG INVESTIGATORS' AWARD to be given by the AMERICAN COLLEGE OF CARDIOLOGY. Competition: Annual Meeting of the College, New Orleans, 1964. Abstracts are due by Dec. 31, 1963. Send to: E. Grey Dimond, M.D., Chairman, Young Investigators Award Committee, Box 1533, La Jolla, Calif.

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Editorial

Murmurs of aortic stenosis and mitral insufficiency masquerading as one another

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The importance of an accurate diagnosis in clinical medicine is obvious. This is certainly true in cardiology Contrary to recent trends toward complex instrumentation and methods in study auscultation by experienced and capable clinicians and cardiologists is accurate simple innocuous and applicable even in the patient's home Important considerations here lie in the interpretation and differential diagnosis of cardiac auscultatory phenomena Even though the subject is a broad one many practical advances in the understanding and application of auscultatory phenomena have been made One special problem which deserves emphasis at the present time concerns the systolic murmurs of aortic stenosis and mitral insufficiency

It is well known but not widely appreciated, that the murmur of aortic stenosis may masquerade as that of mitral insufficiency and conversely that the murmur of mitral insufficiency may masquerade as that of aortic stenosis In this respect, the fallacy of diagnosing the valvular origin of murmurs according to the precordial area of greatest intensity of the murmur is brought into its clearest perspective One finds that in the diagnosis of murmurs the precordial location is the one most frequently used and likewise misused feature Location and transmission of murmurs are of obvious importance but pitfalls must be realized

As a point of orientation the now popular classification of systolic murmurs into the ejection type or the regurgitant type[1,2] merits brief review Exceptions and suggested additions to this classification have been pointed out Briefly ejection murmurs are associated with an altered flow of blood across the semilunar valves Aortic ejection murmurs begin shortly after the first heart sound and end shortly before the aortic second sound These murmurs are limited to the period of ventricular systolic ejection and have a crescendo-decrescendo or diamond-shaped configuration being more intense near mid systole Regurgitant valvular murmurs are not limited to the period of systolic ejec

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tion but are present throughout mechanical systole of the ventricle (holosystolic or pansystolic). The most common cause of this type of murmur in man is mitral regurgitation. It begins with and often obscures the first sound and ends at or slightly later than the aortic second sound. It tends to lack the crescendo-decrescendo quality, having a rather flat or plateau configuration or frequently a gradual late systolic accentuation. These differences in timing of the aortic ejection murmur and the mitral regurgitant murmur cannot be overemphasized. Furthermore, the hemodynamic reasons for these differences are obvious.

Although the murmur of aortic stenosis is usually maximal at the second right intercostal space near the sternum, at times it is also clearly audible at the apex and occasionally it is maximal or even confined to the apex. This obviously causes confusion with mitral insufficiency. Fortunately for the clinician, in such situations of atypical transmission the murmur usually retains its ejection characteristics with a crescendo-decrescendo configuration with peaking in mid-systole and ending shortly before the aortic second sound. Thus not only the precise timing of the murmur but the configuration of intensity also aid in its correct diagnosis and differentiation from mitral insufficiency. Another helpful point is that even though the aortic valvular systolic murmur may be soft to absent at the aortic area, it may be readily detected over the carotid artery in the neck, especially on the right side. It is interesting that at times the murmur of aortic stenosis as it is transmitted to the apical region of the heart may have a distinct musical quality and may or may not be associated with a harsh systolic murmur at the aortic area (Gallavardin phenomenon). It is important to remember this dissociation in frequency components of murmurs which emanate from the same basic anatomic lesion. Thus, when aortic stenosis is suspected, one is less likely to erroneously attribute a musical murmur at the apex to mitral insufficiency. Awareness of this phenomenon and careful attention to other details pointed out herein will help avoid this error.

That the murmur of mitral insufficiency may mimic the murmur of aortic stenosis on auscultation is less well known. Classically, the murmur of mitral insufficiency is considered to be loudest at the apex with radiation to the left axilla and left scapula. Several recent reports, however, have emphasized the fact that occasionally radiation may be toward the base including the second right intercostal space and even the neck, thus simulating the murmur of aortic stenosis.[6-13] It has been suggested that in such instances of atypical radiation to the aortic area, mitral incompetence of primarily the posterior mitral leaflet exists. This tends to direct the regurgitant stream of blood forward and medially against the atrial septum at the base of the aorta with production of a murmur.[14] Thus vibrations set up in the base of the aorta by the jet of blood account for transmission of the murmur to the base of the heart and even into the neck. Evidence for this mechanism is afforded by the detection of jet lesions of the endocardium in this area of the atrium in autopsied patients. Of interest is the increasing number of recent reports of ruptured chordae tendineae in which this mechanism has been advanced to explain the cause of the resulting mitral insufficiency which tends to produce a murmur that simulates the murmur of aortic stenosis.[14,6] In one patient not only was the murmur loud at the aortic area but it also had a distinct diamond-shaped configuration. Recently reported on were two patients with mitral insufficiency, probably due to rheumatic fever, in whom the auscultatory findings simulated aortic stenosis. Although there was no autopsy confirmation, the authors tended to believe that a similar jet mechanism was the cause. They remarked that although murmurs over the precordium and to the right of the sternum are common in extreme mitral insufficiency with a giant left atrium, such was not the case in their patients.

It would appear that in the evaluation of a patient with possible mitral insufficiency masquerading as aortic stenosis, careful attention to auscultatory details can be very helpful. One may find that the murmur at the aortic area is truly holosystolic, i.e., it begins with the first sound and continues to and particularly through

the aortic second sound.[7] This is of considerable value in realizing that the murmur is due to mitral insufficiency. Furthermore, mitral origin is favored when there is no tendency for the murmur to be diamond shaped (mid-systolic accentuation) and when the configuration is plateau, especially *with a tendency to late systolic* accentuation. This latter feature is particularly distinctive of mitral insufficiency. Careful attention to the quality of the murmur is of further help in differential diagnosis, but differences of this nature are more difficult to detect with systolic than with diastolic murmurs. Typically, the murmur of mitral insufficiency is high pitched and blowing in quality, whereas that of aortic stenosis is lower pitched and harsh or rasping. There are frequent exceptions, however.

A murmur of mitral insufficiency which occasionally causes *confusion is that re*cently described which results from mechanical dysfunction (without rupture) of the left ventricular papillary muscles.[20] This murmur is frequently diamond shaped in configuration and, although loudest at the apex, it may occasionally radiate well to the aortic area, possibly *simulating* aortic stenosis.[20] The distinguishing and important diagnostic auscultatory feature, however, is the fact that this is a circumscribed murmur of delayed or late onset beginning after the first heart sound. It is not holosystolic. Furthermore, the electrocard*iogram may be of distinct help in* diagnosing it. Infarction or fibrosis of a papillary muscle is the primary cause of papillary muscle dysfunction of this type and the lesions may be suspected electrocardiographically.[20, 21] In this respect, in the proper clinical setting, true rupture of either the anterolateral or posteromedial papillary muscle may be suspected clinically by electrocardiographic changes and the presence of a mitral insufficiency mur*mur*.[20] The murmur of a ruptured papillary muscle (or its attached chordae tendineae) differs from that of simple papillary muscle dysfunction, however, in that, although the murmur of a ruptured papillary muscle or chordae tendineae may have crescendo-decrescendo characteristics, it is holosystolic, beginning with the first heart sound without delay.[20]

Again considering auscultatory differentiation of the murmurs of mitral insufficiency and aortic stenosis with atypical location, other observations can help. It has been pointed out in patients with aortic stenosis and atrial fibrillation that the intensity of the murmur varies directly with the preceding cycle length, i.e., it is more intense after long pauses and less intense after shorter pauses. In mitral insufficiency this was found not to be the case, since the intensity of the murmur here tends to be less related to the preceding cycle length. It has been suggested that the same reason*ing may be applied equally well to other* irregular rhythms, including premature contractions.[7, 8] In spite of the published reports, in the presence of premature contractions we have noted occasional exceptions to this rule, as have others.

Other auscultatory findings may be *helpful in diagnosis. In mitral insufficiency*, wide splitting of the second heart sound may occur because of the early closure of the aortic valve associated with a decreased duration of left ventricular systole.[22] In the absence of right ventricular decompensation this splitting varies normally (wid*ens) with inspiration*.[22] However, in aortic stenosis, because of a delay in closure of the aortic valve, the second sound may be only narrowly split and indeed show a reversed split (closure of the pulmonary valve precedes closure of the aortic valve). In the latter situation paradoxical splitting *would occur on respiration*, i.e., a widening of the split on expiration and a narrowing on inspiration.

Observations concerning the intensity of the mitral first heart sound and the aortic second sound may also be helpful. In pure mitral insufficiency (without mitral stenosis) with *incompetence of both leaflets* the first sound would tend to be soft and merged with the loud systolic murmur,[23] whereas in aortic stenosis this would not be expected. In an evaluation of the intensity of the first heart sound the effect of atrioventricular conduction time (P-R interval) must be considered. *With respect* to the aortic second sound, classically, the intensity should be reduced in aortic stenosis, whereas in mitral insufficiency *it should* be relatively normal. Exceptions to these generalizations are well known.

Although infrequently required, one procedure which is practical for bedside auscultation and which can be useful in differential diagnosis, is the amyl nitrite test.[23] Briefly, careful auscultation is done during and immediately after the patient inhales the amyl nitrite. The murmur of mitral insufficiency becomes softer and shorter during and for approximately 20 seconds after inhalation. Conversely, the murmur of aortic stenosis becomes louder after inhalation and reaches a peak intensity at approximately 30 to 45 seconds.[23] Pharmacologic manipulation of murmurs has also been done by the use of vasopresser agents. In general, these agents cause changes which are the opposite of those produced by amyl nitrite.

Lastly, in the clinical analysis of the problem of atypically localized murmurs of aortic stenosis and mitral insufficiency, one should take into consideration the many clues gained through a complete clinical evaluation. It is difficult to define the degree to which these should influence the diagnosis, but their significance in the purest sense is well known. These observations include arterial blood pressure, pulse pressure, type of pulse, roentgenographic localization of valve calcification, of specific chamber enlargement or of vascular change, electrocardiographic changes, the presence of detectable associated lesions, and many others. All of the clinical data should be considered, among which auscultation is an integral part.

In summary, if one relies solely on the characteristic of location for the determination of the specific valvular origin of murmurs, gross errors will occasionally be made. Careful and thoughtful attention to detail must be exercised in order to avoid these pitfalls.

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Clinical communications

The significance of late systolic murmurs

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Although it is generally agreed that an apical pansystolic murmur with late systolic accentuation is due to mitral incompetence, the late systolic murmur which has no early systolic vibrations demonstrable on a phonocardiogram has been regarded as innocent and probably extracardiac[1] in origin. Late systolic murmurs are not rare and their innocent significance has been supported by the usual absence of electrocardiographic or radiologic evidence of cardiac abnormality. These murmurs are often accompanied by a mid or late systolic click which has also been regarded as extracardiac in origin.[4, 9-12] Leatham[12] has recently claimed that the murmur which is confined to late systole is likely to be entirely innocent for this curious timing does not fit our present knowledge of hemodynamics. McKusick has observed that late systolic murmurs sometimes extend beyond the aortic component of the second heart sound and he believes that this, together with the mid late systolic clicks which are often associated, provide evidence that late systolic murmurs are of pericardial origin.

A pansystolic murmur with late systolic accentuation implies that there is an increased amount of regurgitation in late systole in spite of a decreasing pressure gradient between the ventricle and the atrium at that time. This must result from some anatomic deformity of the mitral valve which makes it more incompetent during this period. It seems logical therefore that in the presence of mild mitral valve disease regurgitation could occur *only* in late systole and that in such instances a phonocardiogram would show only a late systolic murmur without early systolic vibrations.

It is the purpose of this paper to show that apical late systolic murmurs whether they be pansystolic with late accentuation or entirely confined to late systole, denote mild mitral regurgitation. The possible cause and significance of the commonly associated systolic clicks are briefly discussed.

Material and methods

Seven patients with apical late systolic murmurs on clinical auscultation were selected for investigation (Cases 1 7 Table

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1). All had been referred to this Cardiac Clinic because of the murmurs although none had genuine cardiac symptoms. The murmurs were fairly soft and never louder than Grade 3 in intensity. Three patients (Cases 4, 6, and 7) had audible mid or late systolic clicks and in a fourth patient (Case 5) a click had been heard and demonstrated by phonocardiography 2 years previously. A past history of rheumatic fever was obtained in 4 patients (Cases 2-5) and in 2 of these (Cases 2 and 3) a soft but very short mid-diastolic murmur was heard at the apex in the left lateral position. The radiologic and electrocardiographic appearances were completely normal in 4 patients (Cases 1, 2, 5, and 6), whereas one (Case 4) had a mild first-degree heart block (P-R interval of 0.23 second) and another (Case 3) had minimal left atrial enlargement radiologically. The last patient (Case 7) had an abnormal electrocardiogram in that the T waves were inverted in Leads II, III, aV$_F$, and V$_6$. Radiologic evidence of slight left atrial and left ventricular enlargement was also present.

Phonocardiograms were recorded on all patients, using both a Sanborn Twin Beam Cardiette and a New Electronic Products (N.E.P.) multichannel apparatus. A microphone was placed over the site of maximum intensity of the murmur with the patient lying in the left lateral position. Particular care was taken to increase the volume to a high level in order to record low-intensity vibrations which may have been present in early systole.

Left ventricular cineangiography. Cineangiography using a 35-mm. Arriflex camera mounted on a 9 inch image intensifier was performed on all 7 patients. After percutaneous puncture of the right femoral artery, a yellow Odman-Lehman catheter,[3] in which four side openings had been made within 1 inch of the tip, was introduced by the Seldinger technique and manipulated through the aortic valve. The catheter was positioned in the left ventricle with the tip directed away from the mitral valve ring. Approximately 35 c.c. of 76 per cent Urografin was then injected with a Talley pressure injector[17] set at 55 to 65 pounds per square inch. The camera was run at a film speed of 32 frames per second with the patient placed in the right and later the left anterior oblique positions. Film was run until dye was seen to have emptied from the left ventricle.

Alteration of circulatory hemodynamics. The effect on the systolic murmurs of altering the hemodynamic state with inhalation of amyl nitrite, a Valsalva maneuver, and the injection of phenylephrine was ascertained and these procedures were used as follows.

A. INHALATION OF AMYL NITRITE. Amyl nitrite was administered on at least three occasions to all 7 patients. Inhalation usually lasted 5 to 12 seconds, and a continuous phonocardiogram was recorded on the Sanborn Twin Beam from the onset of inhalation until about 2 minutes thereafter. The procedure was then repeated on the N.E.P. apparatus and short tracings at a paper speed of 80 mm. per second were made at about 10-second intervals. In this way we were certain of observing all the changes in the intensity and timing of the murmurs which occurred.

B. VALSALVA MANEUVER. The effect on the systolic murmurs of a 10 to 15-second Valsalva maneuver was assessed in all but one patient (Case 1). Esophageal and arterial pressures were not recorded, but we were satisfied that an effective Valsalva maneuver had been performed in each instance. The procedure was repeated on several occasions and the response of the systolic murmur was noted through the audiophone of the phonocardiographic apparatus. In addition, a phonocardiographic tracing was taken before, during, and for approximately 16 seconds after the straining period on at least two occasions in each patient tested.

C. INJECTION OF PHENYLEPHRINE. An intravenous injection of 1 mg. of phenylephrine was given to 4 patients (Cases 2-5). Blood pressure readings (cuff method) and phonocardiograms on the N.E.P. apparatus were taken before injection and at 20 to 30-second intervals thereafter until the effect of the drug had worn off—usually within 4 to 6 minutes.

Results

1. *Phonocardiograms.* In 6 patients the systolic murmurs were crescendo-decrescendo in shape and reached maximal in-

tensity just before the aortic component of the second heart sound (Cases 1-6, Fig 1). Vibrations sometimes extended just beyond the aortic closure sound. In 3 instances low-intensity vibrations were also shown during early systole and the murmurs were thus pansystolic (Cases 1, 2 and 4, Fig 1) but in the other 4 (Cases 3, 5–7, Fig 1) the murmurs were confined entirely to mid-late systole. The last patient differed from the rest in that decrescendo vibrations were present which entirely followed a late systolic click (Case 7, Fig 1). Mid-late systolic clicks were well demonstrated in 2 other patients, although in these the vibrations *preceded* as well as followed the clicks (Cases 4 and 6, Fig 1).

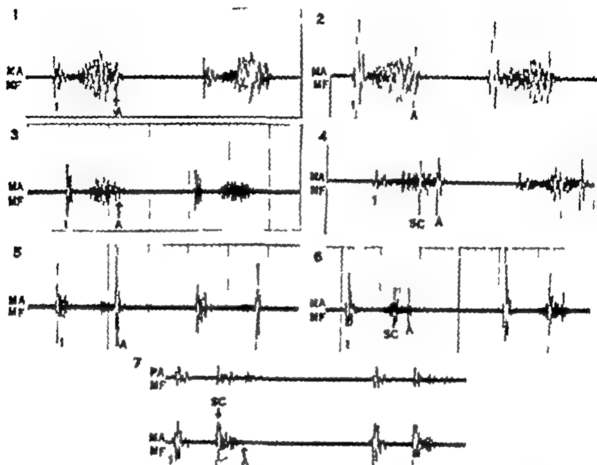
2. *Left ventricular cineangiography.* Regurgitation of the radiopaque dye from the left ventricle into the left atrium occurred during ventricular systole in all 7 patients. The amount of dye which entered the left atrium was surprisingly large in the patients with pansystolic murmurs whereas in those with murmurs confined to late systole a small jet was seen with each ventricular systole. The regurgitation in all instances was observed during at least three ventricular contractions in both the right and left anterior oblique views.

It has been shown in dogs[18,19] and occasionally in man[20,21] that regurgitation of dye through normal mitral valves may take place during prolonged *diastolic* periods, such as may occur with bradycardia, the compensatory pause after an ectopic beat, or a period of asystole.[19] Such disturbances in rhythm are not uncommon during the injection of radiopaque substances into the left ventricle. However, unlike true mitral incompetence in which progressive opacification of the atrium occurs with each ventricular systole,[22] the dye which regurgitates during prolonged diastasis disappears from the atrium as soon as normal rhythm is restored.[20,22] We are also satisfied that dye was not injected directly into the left atrium and that the catheter did not interfere with the function of the mitral valve since the tip was always placed in a position well away from the valve ring.

We have performed left ventricular cineangiography in 25 patients with no clinical evidence of mitral incompetence and in no instance has regurgitation of dye into the left atrium been observed. Other

Table 1 Data on patients subjected to left ventricular cineangiography

Case	*Sex*	*Age (yr)*	*Previous rheumatic fever*	*Type of late systolic murmur*	*Mid-late systolic click*	*Associated apical murmurs*	*X-ray*	*ECG*
1	M	37	No	Grade 3 pansystolic	Absent	Nil	Normal	Normal
2.	M	27	Yes	Grade 3 pansystolic	Absent	Soft, short mid-diastolic	Normal	Normal
3.	F	31	Yes	Grade 3 late systolic	Absent	Soft, short mid-diastolic	Left atrial enlargement	Normal
4.	M	30	Yes	Grade 3 pansystolic	Present	Nil	Normal	P R interval 0.23 sec
5	F	20	Yes	Grade 1 late systolic	Absent. Demonstrated on phonocardiogram 2 yr previously	Nil	Normal	Normal
6.	F	29	No	Grade 1 late systolic	Present	Nil	Normal	Normal
7	F	48	No	Grade 2 late systolic. Decrescendo. Followed click	Present	Nil	Left atrial and left ventricular enlargement	T-wave inversion in Leads II, III, V



F 1 Phonoc d gram of the 7 patient (the number next to each tracing correspond to the se numb a Table I) th peal lat systolic murm C ses 1 2 nd 4 ha pansystolic durations. The tolic murmurs of Cases 1-6 re crescendo-decresc ndo w th lat systolic ac entuation. The systolic murmur of Case 7 entirely f llows ystolic lick nd is decrescendo in shape *MA* Mitral area *PA* P lmonary rea. *MF* Medi m frequency *A* Aortic omponent of the second heart sound. *SC* Systolic click Time ters l between the hea y ert al lines 0 2 second

workers[35,36] using similar techniques have also not shown r liologic evidence of true mitral incompetence in patients in whom this was not suspected Thus we consider that the regurgitation of dye shown in our 7 patients provides conclusive evidence of true mit al incompetence

3 Effects on the systolic murmurs of hemodynamic alterations

A INHALATION OF AMYL NITRITE The hemodynamic changes which result from the inhalation of amyl nitrite have been fully studied by Beck and associates[36] Immediately after inhalation and for a period lasting about 60 seconds there is a significant drop in the systemic pressure Tachycardia occurs a few seconds after the hypotension and this results in an increased venous return to the right side of the heart Cardiac output increases and the stroke volume is either unchanged or increased[36] During the period of systemic hypotension the regurgitant systolic murmur of mitral incompetence characteristically decreases in intensity[35,37] and then returns to the control intensity as the blood pressure rises again

In all 7 patients a definite and marked decrease in the intensity of the systolic murmur occurred during the first 15 seconds after inhalation A feature which we ourselves have not observed nor seen reported in other forms of systolic murmur due to mitral regurgitation was that about 20 to 50 second after the inhalation of amyl nitrite the systolic murmur developed

maximal accentuation in mid-systole and in all but one instance (Case 1) the total vibrations seemed to be of greater intensity than during the control period (Fig 2) This change develops slowly and almost certainly represents an alteration in timing and intensity of the late systolic murmur and is not an ejection systolic murmur brought out by the amyl nitrite. The earlier accentuation and increased intensity of late systolic murmurs after amyl nitrite have been observed previously by Vogelpoel and associates, but it should be emphasized that the very early *decrease* in intensity of the murmur will be missed unless phonocardiography is started within 15 seconds of the first inhalation of the drug

B. VALSALVA MANEUVER. During the straining phase of a Valsalva maneuver venous return to the heart is decreased and the mean arterial blood pressure falls.[22,29] After release there is a further sudden drop in systemic pressure, probably accounted for by direct transmission of the marked fall in intrathoracic pressure at this time[3] and then with the increase in venous return a progressive rise in systemic pressure occurs until it often exceeds the control level. This is the time of the so-called over shoot, which is usually followed by reflex bradycardia [8]

In has been shown[30] that both left sided and right-sided murmurs decrease in intensity during the straining period On release of straining right-sided murmurs regain their original intensity immediately whereas the return of murmurs which arise in the left side of the heart is delayed by the time taken for the blood to pass through the lungs.[30,31] Left-sided regurgitant systolic murmurs would thus be expected to return to their control intensity about 4 to 11 beats after release of straining

In all 6 patients in whom the effects of a Valsalva maneuver were studied the systolic murmur decreased in intensity during the straining phase and on release returned to normal after a delay of at least 4 beats (Fig 3) An actual increase in the intensity of the murmur above the control value was observed in 3 patients during the post straining period This was associated with a bradycardia and presumabl resulted from a rise in systemic pressure. The response to the Valsalva maneuver was confirmed phonocardiographically in all but one patient. In that instance the murmur was so soft (Case 5 Fig 1) that it was obscured by vibrations due to muscle tremor and breath sounds. These extraneous noises invariably accompany a Valsalva maneuver and other workers[19] have noted that it

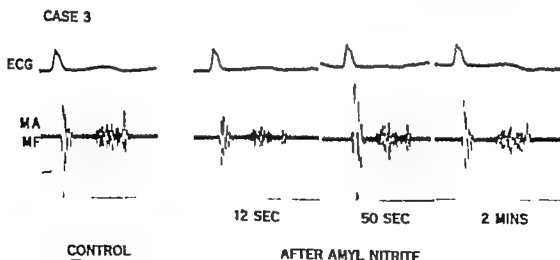


Fig 2 Phonocardiogram of Case 3 before nd t intervals after the onset of inhalation of amyl ltrite. At 12 seconds the systolic murmur is softer and occurs earlier in systole. At 50 seconds the murmur is till earlier but is slightly louder than the control.

is considerably easier to detect the alterations in murmurs and heart sounds on auscultation than it is to demonstrate them on a phonocardiogram Therefore the conclusion is that the systolic murmurs of the 6 patients tested responded to the Valsalva maneuver in a manner compatible with that of the regurgitant systolic murmur of mitral incompetence

In addition to the decreased intensity of the systolic murmur during the straining phase it also appeared that the murmur altered in configuration and became loudest in mid-systole (Fig 4)

C INJECTION OF PHENYLEPHRINE The intravenous injection of phenylephrine causes a temporary rise in systemic blood pressure and a reflex bradycardia. Therefore a systolic murmur of mitral incompetence increases in intensity during the hypertensive period[illegible] Such an increase in intensity was shown in all 4 patients to whom this drug was administered It was noteworthy however that the configuration and time of maximal intensity of the murmur remained unchanged (Fig 5)

The common association of mid-late systolic clicks

It has often been assumed that mid late systolic clicks are invariably extracardiac in origin[illegible] and their common association with late systolic murmurs has been taken to imply that the latter also arise extracardially [illegible] Having shown that the systolic murmurs are due to mitral incompetence we have to consider that the clicks are likely to arise from an intracardiac cause In a recent discussion on the possible origin and significance of mid late systolic clicks Reid[illegible] postulated that they might sometimes be caused by abnormal chordae tendineae of the mitral valve and he suggested that such chordae may or may not be associated with mitral regurgitation. The accuracy of Reid's postulation is supported by the necropsy observation made several years ago by one of us (J B B) of a single fibrosed mitral valve chorda in a patient who in life had had an isolated mid-systolic click. We do not deny that pleuropericardial adhesions as originally described by Gallavardin[illegible] are sometimes the only abnormal cardiac finding at necropsy in subjects who had had a mid-systolic click, and we have in fact recently seen such a case in a woman who died from uremia. In addition to the 4 patients (Cases 4-7) in this series however we have encountered 6 others in recent months who had late systolic murmurs with mid-late systolic clicks and it seems unlikely that this relatively large number of patients should have extracardiac clicks in association with mild mitral incompetence Furthermore we have recently observed the development of loud mid systolic clicks in 3 patients after mitral valvotomy in one instance the click was heard within 48 hours of operation This early occurrence is more compatible with a fibrosed chorda which produces the click after mobilization of the valve cusps than with the alternative possibility of the formation of a pleuropericardial tag The fact that we have not yet observed the development of a mid-systolic click in any patient after operation for congenital heart disease would also favor this postulate

A more detailed report on the changes in timing and intensity of systolic clicks in response to altered hemodynamic states will be the subject of a further communication At present we are impressed by the changes produced by the inhalation of amyl nitrite the Valsalva maneuver and the injection of phenylephrine and it seems probable that their fairly constant pattern is more compatible with an intracardiac than with an extracardiac origin During the systemic hypotensive phase after amyl nitrite, and during the straining phase of a Valsalva maneuver the clicks often move to an earlier position in systole A decrease in intensity also occurs during the Valsalva maneuver but this alteration is inconstant after amyl nitrite Phenylephrine causes no significant change in the timing of the clicks, but their sudden disappearance is a common feature during the hypertensive period.

General discussion

Whether or not an apical late systolic murmur is shown phonocardiographically to have additional early systolic vibrations it seems certain that the regurgitation in late systole must be explained on the basis that the mitral valve is either only incompe

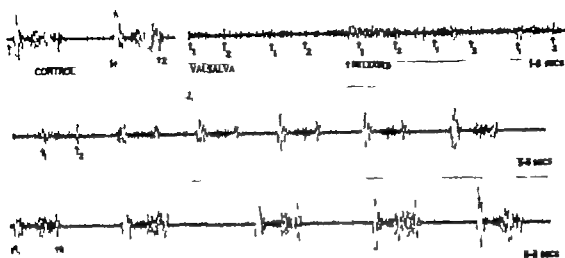


Fig. 3 The effect of V [illegible]alsalva maneuver on late systolic murmur. The last 2 beats of the straining phase are seen, followed by continuous phonocardiogram until the murmur returns to control intensity at least 10 beats and 9 seconds after release of straining. The decreased intensity of the systolic murmur is clearly seen. The positions of the first and second heart sound are marked at the time when extraneous noises predominate.

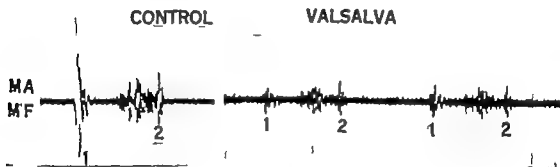


Fig. 4 Phonocardiogram demonstrating the earlier accentuation as well as the decreased intensity of late systolic murmur during the straining phase of Valsalva maneuver.

tent or more incompetent at this time. There seems to be little justification therefore to differentiate a pansystolic murmur with late accentuation from one which is confined to late systole other than to appreciate the fact that the former represents a mitral valve which is incompetent throughout systole. We have in fact seen 2 patients, both middle-aged women in whom *systolic murmurs spontaneously* altered after a period of several months. In the first, a late decrescendo systolic murmur which originally completely followed a click, later developed vibrations in early systole, whereas in the second patient the early vibrations of a pansystolic murmur with late accentuation completely disappeared.

It is possible that fibrosed chordae tendineae are responsible for increasing, or causing the incompetence in late systole but this must at present remain speculative. In one patient (Case 6) the late systolic murmur became almost pansystolic with mid-systolic accentuation in the beat which followed the compensa

ECG
CASE 5
MA
MF

125/90 CONTROL

180/115 160/115 AFTER PHENYLEPHRINE

ECG
CASE 4
MA
MF

120/85

165/110 135/85

Fig. 5. Phonocardiogram of Cases 5 and 4 showing the increased intensity of the late systolic murmurs during the hypertensive period after intravenous phenylephrine.

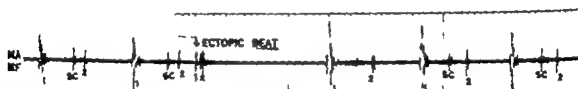


Fig. 6. The effect of an ectopic beat on late systolic murmur and mid-late systolic click (Case 6). It can be seen that the systolic murmur is almost pansystolic after the compensatory pause and that the click is either much softer and slightly earlier or has disappeared at this time. It is likely that the click (marked "X"), followed by few vibrations of the systolic murmur, has moved to a very early systolic position during the ectopic beat.

tory pause after an ectopic beat (Fig. 6). Theoretically, this change in the systolic murmur could depend on either the larger left ventricular diastolic volume or the increased intraventricular pressure. A raised pressure alone, however, as produced by the injection of phenylephrine serves only to increase the intensity of the systolic murmur without altering its shape. On the other hand, 20 to 50 seconds after the inhalation of amyl nitrite, when the left ventricular pressure is still lower than before inhalation but when the stroke volume is possibly greater, the systolic murmur accentuates earlier in systole and may increase in intensity. During the straining phase of a Valsalva maneuver, the systolic murmur again tends to accentuate earlier although at this time the stroke volume must be reduced. It thus seems possible that an alteration in the left ventricular diastolic volume affects the functional

anatomy of the mitral valve in patients with late systolic murmurs and that this results in the change in the time of maximal regurgitation

So-called "cardiorespiratory" murmurs are regarded as a type of innocent extracardiac systolic murmur [35-37] and are reputed [34] to result from pressure of the heart in systole "on a lappet of lung." The cardiorespiratory murmur of Castle and Craige[5] was described as occurring in late systole, and in fact, seems to have been identical to the late systolic murmur which we have studied and shown to be caused by mitral incompetence.

Although it is agreed that a systolic murmur confined to late systole denotes minimal hemodynamic alteration, it was clearly important to establish whether such a murmur is due to mitral regurgitation or to an extracardiac cause. We submit that the evidence proves that mitral incompetence is responsible and that patients with such murmurs should be regarded as potential candidates for subacute bacterial endocarditis. Furthermore, especially in young subjects, it is likely that the mitral valve lesion is rheumatic in etiology and therefore prophylactic antibiotic therapy against further rheumatic activity should be instituted.

Summary

1. Four patients with apical systolic murmurs confined to mid-late systole, and 3 patients with pansystolic murmurs with late accentuation were subjected to left ventricular cineangiocardiography. Regurgitation of dye into the left atrium during ventricular systole occurred in all patients.

2. Inhalation of amyl nitrite, a Valsalva maneuver, and intravenous injection of phenylephrine resulted in a fairly constant alteration in the intensity and the time of maximal accentuation of these murmurs. The conclusion is that the pattern of change is compatible with that of a mitral regurgitant systolic murmur.

3. The common association of late murmurs with mid-late systolic clicks is confirmed and reasons for suspecting that these clicks are due to fibrosed chordae are discussed.

4. The importance of appreciating that late systolic murmurs are due to mild mitral incompetence is stressed. Although little hemodynamic alteration is present, these patients are presumably potential candidates for subacute bacterial endocarditis and in younger patients prophylaxis against rheumatic activity is indicated.

Addendum

Since this paper was submitted for publication, we have performed left ventricular cineangiography in a 44-year-old man with a soft apical murmur confined to late systole. Mild regurgitation of dye from the left ventricle to the left atrium was again clearly seen during ventricular systole, and thus the diagnosis of mitral incompetence was confirmed.

It has not seemed to be justifiable to perform left ventricular angiography, a relatively major procedure, in other patients with apical late systolic murmurs, but we have observed the effect of phenylephrine, amyl nitrite, and a Valsalva maneuver in 8 such patients as well as in the 44-year-old man referred to above. In all instances, responses similar to those described in this paper were encountered and particularly impressive was the marked increase in intensity of the murmur after injection of phenylephrine. These results strongly suggest, therefore, that all the additional 8 patients also have mild mitral regurgitation.

Seven of these 8 patients had an associated mid-late systolic click, and this high incidence is again compatible with the postulate that fibrosis of mitral chordae tendineae is the cause of these clicks.

We wish to thank Professor G. A. Elliott for his encouragement in the preparation of this paper and Dr. K. F. Mills, Superintendent of the Johannesburg General Hospital, for permission to publish. We gratefully acknowledge the assistance of our technicians, particularly Miss W. Findlay and Miss E. Isaacs. We also wish to thank Mr. A. Shevitz, Mr. E. G. Seering and Mr. H. Kruger of our Photographic Unit for the photographs.

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Electrocardiographic features in clinical and experimental ventricular pre-excitation

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Short P R interval with wide QRS complex was reported as early as 1915 but was recognized as a clinical and electrocardiographic entity only in 1930 by Wolff Parkinson and White.[2] However even in the original article, one could see that in addition to the characteristic features of the first part of the QRS complex there are marked alterations in the height of the R wave and also in the terminal portion of the QRS complex, namely disappearance of a previously existing S wave Furthermore there is a depression of the S-T segment and inversion of the T wave. An explanation was soon reached by all that the shortening of the P R interval and the appearance of a slowly rising delta wave with normal P J interval indicate premature excitation of a part of the ventricular muscle which results in a fusion beat Since then a number of articles have been published which deal with the possible mechanism which can cause the early depolarization in that part of the ventricle However in regard to the morphology of the QRS following the delta wave not much attention was paid to the above mentioned differences from the tracing obtained during normal conduction Although some authors have described changes in the configuration of the complex and suggestions have been made as to their mechanism of production there is, to date no satisfactory explanation of this phenomenon

Clinical material

The electrocardiograms of 4 patients were studied. Their case histories are presented briefly below

Case 1 M L 28-year-old hard laborer was known to suffer from paroxysmal tachycardia. Such attacks were always precipitated by exertion. Physical examination was noncontributory The electrocardiogram at the time of his admission to the hospital was characteristic for WPW conduction and exhibited very high R waves in Leads I V_L and V_{4-6} The patient was given quinidine 1.6 Gm. per day orally and on the following day the WPW conduction disappeared. The electrocardiogram at this time showed normal voltage of the QRS complexes in each lead and the appearance of S waves in Leads I and V (Fig 1).

Case 2 Z W 26-year-old clerk, was found to have WPW syndrome on routine examination for health insurance. The patient had no clinical history relevant to this abnormality Physical examination revealed normal findings. The electrocardiogram exhibited the characteristic features of WPW conduction. The sum R + S_{V_1} was 56 mm suggesting left ventricular hypertrophy Two days after oral administration of 1.0 Gm. of quinidine, the abnormal conduction disappeared and the electrocardiogram became normal. When Lead V was recorded, alternating WPW beats were observed, and this tracing showed that the deep S waves which were

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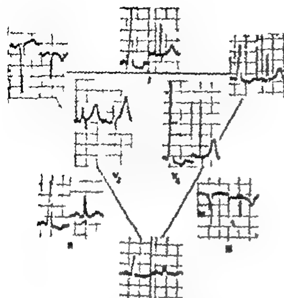


Fig. 1. Case 1. The first beat in each lead was recorded during WPW conduction, whereas the second one was recorded after restoration of the normal conduction. Note High R waves in Lead I, V and V with depressed S-T segment and inverted T during WPW conduction. During normal conduction the tracing is normal. S waves appeared in Lead I and V.

present in the normally conducted beats disappeared almost completely in the WPW beat (Fig. 2).

Case 3. M. D., a 70-year-old clerk, was admitted to the hospital for prostatectomy. The routine electrocardiogram prior to operation exhibited signs of WPW syndrome and marked left ventricular hypertrophy. Administration of quinidine for 4 days obtained the normal conduction and the tracing showed normal pattern with marked diminution of the R waves in Lead I, V and V (Fig. 3).

Case 4. C. N., a 44-year-old housewife, had a myocardial infarction suspected 3 years prior to hospitalization. The patient continued to complain of precordial pain which was brought about by exertion. The diagnosis of coronary artery disease seemed to be justified. The electrocardiogram showed WPW syndrome and signs suggestive of posterior wall infarction. In the presence of suspected coronary artery disease in a patient with WPW syndrome the ventricular gradient was calculated to be −5 degrees, which was abnormally deviated. Normal conduction could be restored by treatment with quinidine 1.0 Gm. per day orally. In addition to the marked changes in the QRS-T in most leads, including diminishing R waves and the appearance of S waves, the signs suggestive of posterior wall infarction also disappeared. However, negative T waves in Lead III and aV appeared. The frontal plane vectorcardiogram showed the marked difference in the direction of the main QRS vector and the terminal portion of the loop (Fig. 4).

The tracings of the patients whose cases are presented above demonstrate that during WPW conduction not only does the P-R interval become shorter and the delta wave appear, but there are remarkable alterations in the height of the R wave and in the terminal portion of the QRS complex. The electrical axis also changes to the left in these cases. One cannot explain these alterations only on the basis of the additional electrical force inscribed during the delta wave since this can influence only the first part of the QRS, but has no effect on the terminal portion. The elevation of the R wave is also out of proportion to the electrical force added by the delta wave.

Bleifer and his co-workers[1] have already emphasized these alterations in the configuration of the complex and their conclusion was that an additional electrical force at the first part of the QRS would not lead to such changes especially in the terminal portion; thus they suggest that the entire conduction is abnormal. Many years previously, Burch and Kimball discussed changes in the magnitude and width of the QRS complex and assumed

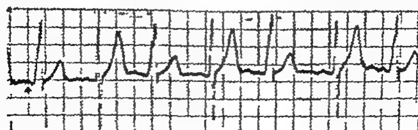


Fig. 2. Case 2. Normally conducted beats are alternating with WPW beats. Note: Markedly diminishing S waves and altered T waves in the WPW beat (Lead V).

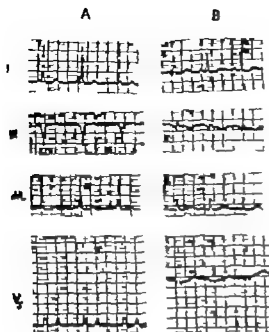


Fig. 3. Case 3. *A*, Tracing during WPW conduction shows high R waves in Leads I and V. *B*, Normal voltage of the R waves during normal conduction.

that altered cancellation may be the cause for it. They did not develop this assumption further and also they did not mention the changes in the terminal portion.

It seemed to us that altered cancellation may explain both the increase in the height of the R wave and the disappearance of the S wave during the pre-excitation syndrome.

The R wave may increase in height either by additional force added in the same direction or by lack of cancellation by contradirectional force or by the action of both these mechanisms. It is well documented that in the WPW syndrome there is such an additional force, the delta wave, the direction of which is almost identical with the main QRS. Most cases of WPW syndrome (mainly of type B) exhibit marked left axis deviation with tall R waves in the left precordial leads. Thus, the delta wave acts either in the right ventricular wall from epicardium to endocardium or in the septum from right to left or in the left ventricle from endocardium toward epicardium. Since the change observed in the R wave is out of proportion to that attributed to the delta wave the other factor, decreased cancellation, seems to be important. The possibility of spread from endocardium to epicardium in the left ventricle will not be likely therefore since altered cancellation in such a case would not augment the R wave to the left. Were the source of the delta wave in the septum directed from right to left (in contrast to normal) it would further enlarge the R wave by altered cancellation in addition to the added delta force. However it would not cause marked change in the terminal portion of the QRS, as observed, since normally the septum contributes mainly to the first part of the complex. It seems, therefore, that in those cases in which the height of the R wave is out of proportion to the added delta wave, and there is a

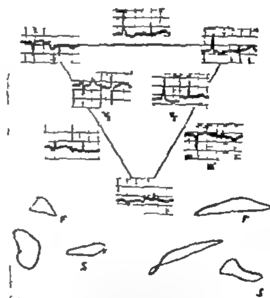


Fig. 4. Case 4. The first beat in each lead was recorded during WPW conduction, whereas the second one was recorded after restoration of the normal conduction. Note ST-T changes in Leads I, V_L, and V_6, and signs which suggest posterior wall infarction during WPW conduction. During normal conduction the S-T segments became normal and the R waves diminished markedly and small S appeared in Leads I and V_L. Leads III and V do not indicate infarction, but the T waves became negative. The heavy lines in the drawings of the vectorcardiogram indicate the delta wave, which is almost in the same direction as the main loop. See the marked change of direction of the QRS loop and its terminal portion during WPW conduction (*right*) when compared to the vectorcardiogram recorded during normal conduction (*left*).

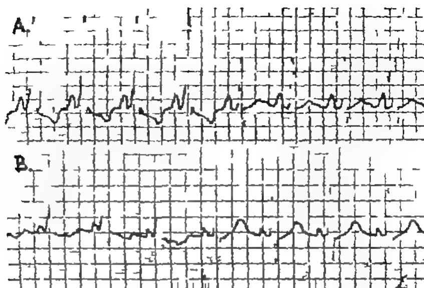


Fig. 5. Tracings A and B were obtained in different dogs. In both the pre-excitation was applied to the subepicardial surface of the right ventricle close to the A-V ring. Note the similarity of the electrocardiographic features during pre-excitation to those characteristic for WPW syndrome. In addition, marked changes in the voltage of the R and S waves are seen.

marked change in the terminal portion of the QRS; these changes might be best explained by one's assuming pre-excitation of the right ventricular wall from the epicardium toward the endocardium.

Since in patients the source and direction of the delta wave can only be suggested but not proved, an experimental study was planned in order to obtain electrocardiographic tracings of fusion beats which resembled the morphology of WPW beats in patients. By this method we attempted to clarify whether pre-excitation of the right ventricle from epicardium to endocardium would result in the same type of changes as seen in the clinical material.

Experimental study

Material and methods. Eight mongrel dogs which weighed between 8 and 18 kilograms were used in this study. They were anesthetized by intraperitoneal administration of sodium Pentothal (35 mg. per kilogram). Ventilation was maintained by a mechanical respirator. The chest was opened by a mid-sternal split, and a longitudinal incision of the pericardium exposed the right atrium and the anterior surface of both ventricles. Ventricular pre-excitation was carried out, similar to the method of Butterworth and Poindexter in the following way.

A bipolar metal needle electrode (2 mm. distance) was applied to the right atrium near the sinus node. The electrical activity was recorded and also fed into a stimulator

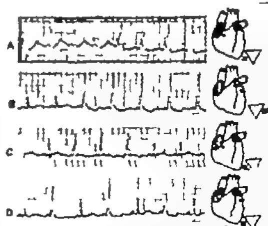


Fig. 6. Some characteristic tracings obtained in different dogs. Note in A and D the disappearance of the S wave, heightening of the R wave, and ST-T changes in the WPW-like beats, and in B and D the very marked rise in the R wave and ST-T changes in the WPW-like beats. The site of excitation and the lead used are shown at the end of each tracing. Paper speed is 50 mm. per second.

This, in turn, produced electrical impulse, the voltage and duration of which could easily be changed, as well as the time lag from the triggering atrial activity. The output of this stimulator was recorded and also led to an isolation unit to reduce the area of ventricular excitation. From the isolation unit the wave of excitation was transferred to the subepicardial surface of the ventricle by means of a bipolar metal needle electrode (2 mm. distance). The sites of excitation were different even in the same dog. The normal conduction system of the dog's heart was untouched.

In most instances, early depolarization was reached by applying 10 volts of 0.02 sec. duration with a delay of 0.04-0.06 sec from the beginning of the atrial potential. Electrical flow was about 0.2 Ma.

Standard bipolar leads were used to record the electrocardiograms of the dogs. Sometimes the electrodes were interchanged to record positive delta deflections, according to the site of excitation.

The artificial respiration was stopped during the recording in order to abolish wandering of the base line. The paper speed was 50 mm. per second.

Results. Thirty-seven electrocardiographic tracings which exhibited all the characteristic features known to occur in the pre-excitation syndrome were obtained in the 8 dogs. In 3 of the dogs, ventricular tachycardia occurred after some successful tracings had been recorded and this soon terminated in ventricular fibrillation. Development of this arrhythmia was due to a technical fault in operating the electronic equipment.

The application of the early electrical excitation to the subepicardial layer of the ventricular wall resulted in marked changes in the electrocardiographic tracings. In addition to the shortening of the P-R interval and the appearance of a slowly rising delta wave, the voltage of the R wave increased, the previously existing S wave decreased or disappeared, and the T wave became negative. The interval between the beginning of the P wave and the rapid ascent of the QRS was equal to the normal P-R interval, whereas the P-J interval remained unchanged. The electrical axis deviated always in the direction of the spread of the early excitation. Right ventricular excitation caused a left axis shift, and left ventricular excitation produced right axis deviation. Figs. 5 and 6 show some representative tracings.

Discussion

In order to explain alterations of the resultant QRS complex in the presence of two electrical impulses reaching the myocardium, one must know where these electrical excitatory forces reach the muscle. There is no doubt that a part of the impulse enters the myocardium via the normal untouched conduction tissue. As to the site of action of the early depolarization of the myocardium, which is the characteristic feature of WPW conduction, various assumptions have been made.

According to the theory of accelerated conduction, a part of the impulse travels through a diseased A-V node faster than the rest of the excitatory wave.[12] This would result in premature depolarization of the free ventricular wall, but the direction of the spread of impulse would remain equal to that during normal conduction, i.e., toward the epicardium. If this were to happen in the right ventricular wall, the delta wave would be in the direction opposite to the main QRS complex. In fact, it is known that the delta wave is always almost parallel to the main deflection. If, however, the early depolarization were to act from the endocardium of the left ventricular wall, the altered cancellation would only augment forces to the right and not to the left as observed. These contradictions seem to rule out the validity of the theory of accelerated conduction.

Some authors have suggested the existence of a hyperexcitable center somewhere in the myocardium, which they consider to be the cause of premature excitation of a circumscribed area of the myocardium.[13] We do not think that such a center can be located in the septum, since its discharge would not result in alterations in the terminal part of the QRS complex. Although it is known that a previously existing S wave may disappear during WPW conduction, septal excitation can hardly be responsible for this, since it does not normally contribute to the build-up of that part of the QRS complex.[4]

If such a hyperexcitable center were located in the subepicardial layer of the free ventricular wall the spread of excitation would be from the outside toward the endocardium The same direction of early depolarization exists also according to the theory of anomalous conduction via the bundle of Kent[3,4] There is no significant difference between these two hypotheses (except for the site of origin of impulses) in regard to the mechanism of the effect of the pre-excitation on the morphology of the QRS complex. We are inclined to accept this direction of excitation— from epicardium to endocardium— as the most likely explanation for the electrocardiographic changes during WPW conduction

On the basis of the cancellation theory according to which equal amounts of electrical forces from opposite directions neutralize each other one can accept that lack of excitation of a part of the ventricular myocardium will augment the resultant main QRS spreading in the opposite direction Early excitation of the same portion in the same direction as the main vector augments it even further Therefore premature excitation from epicardium to endocardium might explain the usually observed increased voltage of the R wave in WPW conduction which is out of proportion to the electrical force added by the delta wave alone The changes in the terminal portion of the QRS complex in this syndrome are also explained by the above-mentioned mechanism The refractoriness of the early depolarized myocardium during the arrival of the main stimulus from the endocardium prevents the participation of the subepicardial layer in the build up of the terminal QRS thereby changing it from the normal pattern

The above-described theoretical considerations seem to elucidate the electrocardiographic changes observed in our patients in whom tracings could be obtained during normal conduction According to Leads I and V_6 in all of our patients the early excitation could have started in the subepicardial layer of the right ventricular myocardium and thus its spread to the left caused left axis deviation and marked increase in the R waves in these leads The observed S-wave changes also fit into the suggested mechanism

Since this explanation which is based on electrocardiographic morphology was acceptable only if the suggested site and direction of the pre-excitation was correct (a condition which could not be proved in the patients) we believed that it was necessary to test the validity of our assumption by producing experimentally fusion beats which resembled in configuration those found in WPW syndrome As anticipated not only was WPW like morphology produced but also the electrical axis deviated in the direction of the delta wave the R wave markedly increased in height when recorded in leads parallel to the delta wave and the previously existing S wave disappeared These changes are identical with those described in our patients, not only qualitatively but also in their relative magnitude

Subepicardial pre-excitation in the experimental animal causes the same configuration of the electrocardiogram as that in patients with WPW syndrome including tall R waves and changes in the terminal portion—and these changes can be explained by altered cancellation It is possible therefore that in the patients with WPW syndrome a similar mechanism prevails in the production of the characteristic electrocardiographic features which thus, the suggested altered cancellation might explain

Summary

Marked electrocardiographic changes, as observed in a comparison with tracings obtained during normal conduction, are described in 4 patients during WPW conduction These changes consisted of an increase in the R wave diminution of the S wave ST T changes and left axis deviation in addition to the short P R and the delta wave

Production of fusion beats in the experimental animal by pre-excitation of the ventricle from epicardium to endocardium revealed electrocardiographic features which resembled those seen in patients with WPW syndrome. These changes included a markedly increased R wave and alterations in the terminal portion of the QRS complex.

It is suggested that if the premature excitation spreads from the epicardium to the endocardium, it augments the R wave and alters the terminal portion of the QRS by (1) adding electrical force to the main vector and by (2) lack of cancellation due to refractoriness of the prematurely activated ventricular muscle.

Because of the similarity between the electrocardiographic changes in the patients and those in the experimental study the described mechanism of action and explanation may hold true for both.

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Systemic hemodynamic effects of amyl nitrite in normal man

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A century ago nitroglycerin (an organic nitrate) and amyl nitrite were introduced into clinical medicine for the treatment of angina pectoris. The two groups of compounds were commonly referred to as the "nitrites" since the pharmacologic properties of nitroglycerin were attributed to the nitrite formed after its administration. Although it is now generally believed that organic nitrates act without prior reduction to nitrites,[4] this does not necessarily imply different modes of action on the circulation. As nitroglycerin became a standard therapeutic agent, interest in amyl nitrite declined and attention to the pharmacodynamic properties of these compounds was focused on the nitrates. In the more recent past, however, amyl nitrite has become an agent of considerable importance in clinical auscultation of the heart and in the phonocardiographic and physiologic diagnosis of heart disease.[6-] In spite of this renewed interest, little attention has been directed to the hemodynamic effects of amyl nitrite in normal subjects.[17] Accordingly, these studies were designed to permit observations on the systemic circulatory effects of amyl nitrite under conditions similar to those employed when the drug is used in the auscultatory, phonocardiographic, and hemodynamic assessment of the cardiac patient.

Materials and methods

Observations were made on 25 unsedated subjects who were either normal medical students or patients from the medical wards or the Outpatient Clinic. All of those selected were carefully screened to exclude the presence of clinically evident cardiovascular disease. Ten were females and 15 were males, whose ages ranged from 16 to 36 years (mean 25 years). The details of each procedure were carefully explained in an attempt to minimize apprehension. Subjects above the age of 40 years were excluded because of the possibility that the circulatory effects of amyl nitrite might differ in older age groups. All studies were performed with the subjects in the supine position. Indwelling Cournand needles were inserted into a brachial and femoral artery and into a large antecubital vein. Sanborn strain gauges were used for determinations

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of brachial arterial pressure. Mean brachial arterial pressures were electronically integrated. Femoral arterial dilution curves were inscribed during constant withdrawal (24.7 c.c./min.) through a Gilford cuvette densitometer after known amounts of indocyanine green were rapidly injected into the antecubital vein. The afferent connection to the densitometer was PE 160 polyethylene tubing exactly 19 cm. in length fitted with short 18 gauge needle hubs. All tracings were inscribed together with an electrocardiogram on a Sanborn 550 M Poly-beam photographic recorder. The linearity of response of the densitometer and recorder had been previously established with Wratten gelatin filters of known optical density. The dilution curves were calibrated by the method of Fox.[9]

Part I (15 studies). Control observations, generally in duplicate, were made while the electrocardiogram, the mean brachial arterial pressure, and the femoral arterial dilution curve were being recorded simultaneously prior to the administration of amyl nitrite. The subject then inhaled amyl nitrite from a broken phial held lightly over the nose with a small cloth. When the mean brachial arterial pressure had achieved its maximum stable fall (10 to 25 seconds), dilution curves were recorded as described above (Fig. 1). The following data were then derived: cardiac index, stroke index, systemic resistance index, appearance time, and mean recirculation time of the injected indicator. Cardiac output was determined from the dilution curves, using the modified Hamilton formula. Systemic resistance in dynes sec. cm.$^{-5}$ was calculated from the formula

$$\frac{\text{BA m}}{\text{COml./sec.}} \times 1\ 332$$

Left ventricular work, in Kg. M./min. was calculated from the formula

$$\frac{(\text{C.O.} \times 1.055) \quad (\text{BAm} \times 13.6)}{1\ 000}$$

Stroke work, in Gm. M., was calculated by dividing minute work by heart rate.

These parameters were related to body surface by dividing each by the subject's body surface area.

Part II. In order to determine whether the parameters under investigation were influenced by the ventilatory effort during the inhalation of amyl nitrite, the following observations were made in 5 subjects. Control data were recorded as indicated in Part I. The inhalation test procedure was then performed for a minimum of 30 seconds in a fashion identical to that described in Part I but without administration of amyl nitrite. Test data were recorded during the ventilation period as indicated in Part I.

Part III. Since mean arterial pressures were recorded at paper speeds appropriate for the quantification of the dilution curves (2.5 to 5 mm. sec.), these tracings could not be used to study the effect of amyl nitrite on the shape of the brachial arterial pulse. Therefore, additional observations were made in 10 subjects (not included in

Table I. Part I

Parameter	Rate (per min.)	Mean arterial pressure (mm. Hg)	Cardiac index (L./min./M.)	Stroke volume index (c.c./M.)	Systemic resistance index (dynes sec. cm.)	LV minute work index (Kg. M.)	LV stroke work index (Gm. M.)	Appearance time (sec.)	Recirculation time (sec.)
Control	79 (43-108)	91 (66-105)	3.8 (2.3-5.2)	48 (34-63)	745 (380-1,500)	4.6 (2.8-6.4)	60 (32-79)	10.2 (7-15)	15.4 (11-20)
Test	133 (66-165)	56 (44-80)	6.8 (5.1-9.9)	52 (40-69)	241 (131-540)	4.6 (2.6-6.9)	35 (23-64)	7 (5-14)	11.8 (8.7-13.5)
Change	+68	−38	+75	+8	−69	−2	−42	−32	−23
p Value	<0.001	<0.001	<0.001	0.3	<0.001	0.9	<0.001	<0.001	0.01-0.001

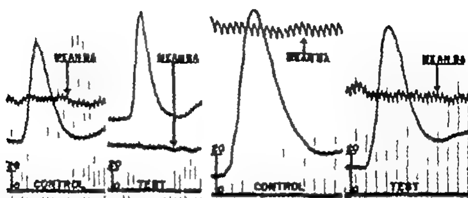


Fig. 1. Two examples of simultaneously recorded mean brachial arterial (*BA*) pressures and quantitative indicator-dilution curves inscribed before and after the inhalation of amyl nitrite.

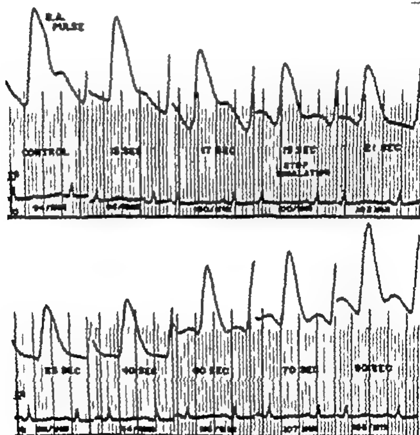


Fig. 2. The brachial arterial (*B.A.*) pressure pulse before, during, and after the inhalation of amyl nitrite.

Part I) while recording the full-scale undamped brachial arterial pressure pulse at paper speeds of 50 mm./sec. (Figs. 2 and 3). Amyl nitrite was inhaled as described in Part I, and continuous recordings were made before, during, and after inhalation. In 5 instances, simultaneous phonocardiograms were taken to record mitral (M.) and aortic (A.) valve closures (Fig. 4) as a measure of the duration of left ven-

tricular contraction.[11] The difference between the duration of contraction (M_1-A_2) and the duration of ejection (onset to dicrotic notch) was considered to be a measure of isometric contraction time. It was then determined whether the post-inhalation decrease in total contraction time could be accounted for by a decrease in isometric contraction alone or only by invoking an associated decrease in the duration of ejection (Fig. 4). This method of estimating the ejection time was necessary since the dicrotic notch disappeared in the postinhalation tracings, precluding direct measurement of the ejection duration (onset of pulse to dicrotic notch). The A_2 to M_1 interval was then measured as an index of the duration of diastole. The pulse tracings were analyzed during the control period and during the period of maximum stable fall in pressure (see Part I). The following information was derived: the rate of rise, the onset to peak, the M_1 to A_2 interval, the duration of ejection, the duration of diastole, the level of the dicrotic notch, the amplitude of the dicrotic wave, and the systolic, diastolic, and pulse pressures.

STATISTICAL ANALYSIS. The data were evaluated by applying Student's *t* test using paired sample analyses rather than the differences between the control and experimental means.[36]

Results

Part I (see Table I). Of the 15 studies included in Part I, 13 yielded valid data. Studies were considered to be invalid if a significant change in mean arterial pressure occurred before complete inscription of the primary dilution curve.

HEART RATE. The average control heart rate was 79 per minute, with a range of 45 to 108. After the inhalation of amyl nitrite the average rate was 132 per minute, with a range of 66 to 165, representing

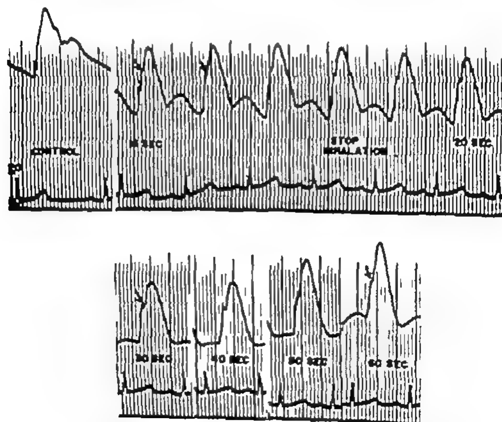


Fig. 3. The brachial arterial pressure pulse before, during, and after the inhalation of amyl nitrite, illustrating the appearance of an anacrotic notch (*see arrows*).

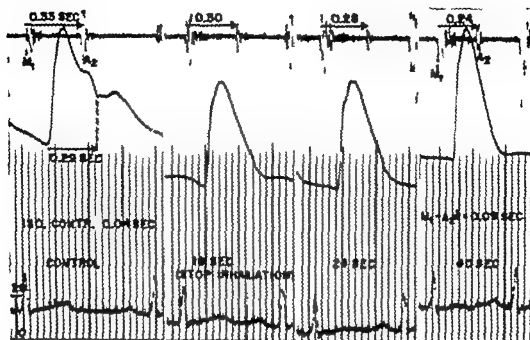


Fig. 4. Simultaneously recorded phonocardiogram and brachial arterial pulse for determination of the duration of left ventricular (LV) contraction (M_1–A interval) in response to the inhalation of amyl nitrite. The control duration of isometric contraction was less than the decrease in the M_1–A interval. The shortening of LV contraction must therefore have been associated with a shortening of the duration of LV ejection.

a significant increase of 68 per cent ($p < 0.001$).

MEAN ARTERIAL PRESSURE. The average control mean arterial blood pressure was 91 mm. Hg with a range of 66 to 105. After the inhalation of amyl nitrite the average mean brachial pressure fell to 56 mm. Hg with a range of 44 to 80, representing a significant decline of 38 per cent over the control value ($p < 0.001$).

CARDIAC OUTPUT. The average control cardiac index was 3.8 L./min./M.² with a range of 2.3 to 5.2. After the inhalation of amyl nitrite the average cardiac index was 6.8 L./min./M.² with a range of 5.1 to 9.9, representing a significant increase of 75 per cent ($p < 0.001$).

STROKE VOLUME. The average control stroke volume index was 48 c.c./M.² with a range of 34 to 65. After the inhalation of amyl nitrite the average stroke volume index was 52 c.c./M.² with a range of 40 to 69, representing an insignificant increase of 8 per cent (p 0.3).

SYSTEMIC VASCULAR RESISTANCE. The average control systemic resistance index was 745 dynes sec. cm.⁻⁵/M.² with a range of 380 to 1,500. After the inhalation of amyl nitrite the average systemic resistance index was 241 dynes sec. cm.⁻⁵/M.² with a range of 131 to 540, representing a significant decline of 69 per cent ($p < 0.001$).

LEFT VENTRICULAR MINUTE WORK. The average control left ventricular minute work index was 4.6 Kg./M./M.² with a range of 2.8 to 6.4. After the inhalation of amyl nitrite the average left ventricular minute work index was 4.6 Kg./M./M.² with a range of 2.6 to 6.9, representing an insignificant decline of 2 per cent (p 0.9).

LEFT VENTRICULAR STROKE WORK. The average control left ventricular stroke work index was 60 Gm./M./M.² with a range of 32 to 79. After the inhalation of amyl nitrite the average left ventricular stroke work index was 35 Gm./M./M.² with a range of 23 to 64, representing a significant decline of 42 per cent ($p < 0.001$).

CIRCULATION TIME. The average control appearance time of the injected indicator was 10.2 seconds with a range of 7 to 15. After the inhalation of amyl nitrite the average appearance time was 7 seconds, with a range of 5 to 14, representing a sig-

nificant decline of 32 per cent ($p < 0.001$). The average control recirculation time of the injected indicator was 15.4 seconds with a range of 11 to 20. After the inhalation of amyl nitrite the average recirculation time was 11.8 seconds, with a range of 8.7 to 13.5, representing a significant decline of 23 per cent (p 0.01-0.001).

Part II. Five valid studies were made.

HEART RATE. The average control heart rate was 68 per minute, with a range of 54 to 81. At the end of 30 seconds of ventilation the average rate was 78, with a range of 60 to 93, a significant increase of 14 per cent ($p < 0.01$).

MEAN ARTERIAL PRESSURE. The average control mean arterial pressure was 98 mm. Hg, with a range of 83 to 110. At the end of the test period the mean arterial pressure was 97 mm. Hg, with a range of 84 to 112, an insignificant change of −0.5 per cent (p 0.6).

CARDIAC OUTPUT. The average control cardiac index was 3.5 L./M./M.², with a range of 2.6 to 4.6. At the end of the test period the average cardiac index was 4.0 with a range of 2.9 to 5.5, representing an insignificant increase of 14 per cent (p 0.05).

STROKE VOLUME. The average control stroke volume index was 51 c.c./M.², with a range of 48 to 57. At the end of the test period the average control stroke index was 51 c.c./M.², with a range of 45 to 58, representing no change (p 0.9).

SYSTEMIC VASCULAR RESISTANCE. The average control systemic resistance index was 774 dynes sec. cm.⁻⁵/M.², with a range of 326 to 1,330. At the end of the test period the average systemic vascular resistance index was 678 dynes sec. cm.⁻⁵/M.², with a range of 294 to 1,224, a 12.8 per cent decrease of borderline significance (p 0.02).

LEFT VENTRICULAR MINUTE WORK. The average control left ventricular minute work index was 4.5 Kg./M./M.², with a range of 3.9 to 6.0. At the end of the test period the average left ventricular minute work index was 5.3 Kg./M./M.², with a range of 4.4 to 7.2, representing a significant increase of 15 per cent ($p < 0.001$).

LEFT VENTRICULAR STROKE WORK. The average control left ventricular stroke work index was 66.2 Gm./M./M.², with a range of 55 to 74. At the end of the test period the average left ventricular stroke work index was 66.5 Gm./M./M.², with a range of 57 to 77, representing no change (p 0.9).

CIRCULATION TIME. The average control appearance time of the injected indicator was 11.0 seconds, with a range of 8.5 to 13. At the end of the test period the average appearance time was 9.5 seconds, with a range of 7 to 11, an insignificant change of −12 per cent (p 0.05). The average control recirculation time of the injected indicator was 16.5 seconds, with a range of 14 to 20. At the end of the test period the average recirculation time was 15.7 seconds, with a range of 14 to 20, an insignificant change of −0.05 per cent (p 0.5).

Part III (*see Table II*). Ten valid studies were made.

ONSET OF RISE TO PEAK OF THE PRESSURE PULSE. The average control interval was 0.10 second, with a range of 0.09 to 0.12. After the inhalation of amyl nitrite the average interval was 0.08 second, with a range of 0.05 to 0.12, representing a significant decrease of 12 per cent ($p < 0.001$).

RATE OF RISE. The average control rate of rise of the brachial arterial pressure pulse was 989 mm. per second, with a range of 462 to 1,550. After the inhalation of amyl nitrite the average rate of rise was 1,152 mm. per second, with a range of 462 to 2,066, representing an insignificant increase of 16 per cent ($p > 0.05$).

INTERVAL BETWEEN MITRAL (M_1) AND AORTIC (A_2) VALVE CLOSURES (DURATION LEFT VENTRICULAR CONTRACTION). The average control interval was 0.32 second, with a range of 0.26 to 0.34. After the inhalation of amyl nitrite the average interval was 0.26 second, with a range of 0.24 to 0.28, representing a significant decrease of 16 per cent ($p < 0.02$). The average decrement in the M_1 to A_2 interval (total contraction time) was 0.052 second. The average preinhalation isometric contraction time was 0.036 second. Thus, we concluded that the duration of ejection decreased.

INTERVAL BETWEEN AORTIC (A_2) AND MITRAL (M_1) VALVE CLOSURES (DURATION OF DIASTOLE). The average control interval was 0.46 second, with a range of 0.30 to 0.58. After the inhalation of amyl nitrite the average interval was 0.26 second, with a range of 0.14 to 0.28, a significant decrease of 57 per cent ($p < 0.02$).

LEVEL OF DICROTIC NOTCH In the control tracings the dicrotic notch averaged 13 2 mm Hg above the diastolic pressure with a range of 11 to 16. After the inhalation of amyl nitrite the notch fell to the level of the diastolic pressure in all instances.

AMPLITUDE OF THE DICROTIC WAVE. The average control height of the dicrotic wave was 4 3 mm Hg with a range of 1 to 5 After the inhalation of amyl nitrite the average height was 0 3 mm Hg with a range of 0 to 1.5 representing a significant decrease of 94 per cent ($p < 0.001$)

SYSTOLIC PRESSURE The average control systolic pressure was 124 mm Hg with a range of 104 to 150 After the inhalation of amyl nitrite the average systolic pressure was 87 mm Hg with a range of 70 to 120 representing a significant decrease of 30 per cent ($p < 0.001$)

DIASTOLIC PRESSURE The average control diastolic pressure was 71 mm. Hg with a range of 62 to 9 After the inhalation of amyl nitrite the average diastolic pressure was 44 mm Hg with a range of 33 to 69 representing a significant decrease of 27 per cent ($p < 0.001$)

PRESSURE PULSE The average control brachial arterial pulse pressure was 54 mm Hg with a range of 34 to 74 After the inhalation of amyl nitrite the average pulse pressure was 44 mm Hg with a range of 30 to 60 representing a significant decrease of 17 per cent (p 0 01-0 02)

Discussion

Amyl nitrite is a drug with acute predictable and short lived action Indicator dilution techniques allow study during the brief period of the drug s maximum systemic hemodynamic effect Although it is realized that a steady state is not achieved under the conditions of these observations [7] it is nevertheless believed that the method permits conclusions in regard to significant directional changes. Test period dilution curves for the estimation of flow were inscribed during the maximum stable fall in mean systemic arterial pressure (Fig 1) This timing was in accord with observations that the increase in cardiac output after the administration of nitroglycerin usually coincided with the nadir of the diastolic pressure Studies were considered to be invalid if a significant change in mean arterial pressure occurred before complete inscription of the primary dilution curve.

Ventilatory effort which approximated that expended during the inhalation of amyl nitrite (see Part II) resulted in a modest increase in the heart rate and cardiac output, with no change in stroke volume and a slight decrease in systemic resistance. Minute work increased slightly but stroke work was unaltered Although the directional changes in heart rate, cardiac output and systemic resistance were similar to those induced by amyl nitrite the magnitude of the ventilatory contribution was small. In our patients, the ventilatory effort was mild and the duration brief (10 to 25 seconds) A significant increase in heart rate and cardiac output, and a significant decrease in peripheral resistance have been induced by hyperventilation [8] but those subjects breathed 40 times per minute for 2 minutes.[9]

Current evidence suggests that the high energy bonds of adenosine triphosphate are of fundamental importance in maintaining smooth muscle tone and contraction [1,20] Both amyl nitrite and nitroglycerin inhibit the activity of ATPase in the rabbit aorta.[20] Interference with enzymatic decomposition of ATP appears to deprive arterial tissue of the energy required for the maintenance of tone thus initiating vasodilatation.[20] In addition to its effect on ATPase, nitroglycerin (but not amyl nitrite) also inhibits oxygen uptake of the rat s aorta implying that it interfers with the aerobic arterial metabolism necessary for resynthesis of ATP Nevertheless the ATP ATPase system appears to be the target enzyme mechanism upon which both nitrites and organic nitrates act to produce arterial relaxation.

Effects on pressure and flow Amyl nitrite caused a striking reproducible decrement in peripheral vascular resistance As the resistance fell the increase in cardiac output was insufficient to maintain systemic blood pressure [16] The fall in peripheral resistance and the associated fall in systemic arterial pressure always preceded the acceleration of heart rate which was therefore reflex tachycardia.[17] Although the cardiac output regularly rose there was little or no change in stroke volume indi

cating that the increase in flow was closely related to the increment in heart rate.

The data do not bear directly on the directional changes in venous return that might be associated with the augmentation in cardiac output. In the dog nitroglycerin has been found to increase the output of the left ventricle to a greater degree than it increased venous return to the right heart, the difference being derived from the thoracic reservoir. It has also been reported that sodium nitrite can dilate systemic capillaries and venules and thus cause a decrease in venous return.[36] This observation has been used to explain the occasional paradoxical action of nitroglycerin in the cardiac patient.[78] On the other hand, Beck and co-workers[1] concluded that the striking increase in right ventricular pressure induced by the inhalation of amyl nitrite in patients with pulmonic stenosis could best be explained by an increase in venous return. These same investigators further believed it unlikely that the reservoir of blood in the thorax was sufficient to permit increases in cardiac output of the degree induced by amyl nitrite without an associated increase in venous return. The increments in cardiac output in our studies were of the same order of magnitude as those reported for amyl nitrite in man[77] but were substantially greater than those reported for nitroglycerin in either man or the dog,[6] except for the ballistocardiographic outputs observed by Wegria and co-workers.

Effects on left ventricular work. The heart performs "work" when it creates pressure to eject blood (pressure work) and when it imparts velocity to blood[77] (kinetic work). Although kinetic work assumes greater importance as flow increases,[4] it is ordinarily performed economically by the heart.[8] Its calculation involves the registration of aortic blood velocity, a technically difficult determination in the human subject. Furthermore only a small portion of ventricular work is ordinarily kinetic (less than 5 per cent), whereas over 95 per cent is expended in developing pressure.[77] Because of these points and because of the practicability of application under our experimental conditions, only pressure work was calculated. The error introduced by using electronically integrated mean arterial pressures was in part fortuitously obviated, since amyl nitrite caused the dicrotic notch to fall to the level of the diastolic pressure, thus rendering systolic mean and electronically integrated mean arterial pressures identical. The decline in systemic arterial pressure induced by amyl nitrite was uniformly associated with an increase in cardiac output sufficient to leave left ventricular minute work relatively unchanged. Since the increment in cardiac output was closely related to the acceleration of heart rate, the left ventricular stroke volume changed slightly, if at all, as the systemic pressure fell. Hence left ventricular stroke work regularly and strikingly decreased.

Effects on the rate of flow and on the shape of the arterial pulse. When the effect of amyl nitrite on the velocity of left ventricular ejection was estimated by measur-

Table II. Part III

Parameter	*Onset to peak* (sec.)	*Rate of rise* (mm./sec.)	*M_1-A interval* (sec.)	*A_1-M interval* (sec.)	*Level of dicrotic notch* (mm. Hg)	*Amplitude of dicrotic wave* (mm. Hg)	*Systolic pressure* (mm. Hg)	*Diastolic pressure* (mm. Hg)	*Pulse pressure* (mm. Hg)
Control	0.10 (0.09-0.12)	989 (462 1,330)	0.32 (0.26-0.34)	0.46 (0.30-0.58)	13.2 (11 16)	4.5 (1 5)	125 (104-150)	71 (62 79)	54 (34-74)
Test	0.08 (0.05-0.12)	1152 (462 2,066)	0.26 (0.24-0.28)	0.26 (0.24-0.28)	0 (0-0)	0.3 (0-1.5)	87 (70-120)	44 (33-69)	44 (30-60)
% Change	−12	+16	−16	−57[?]	−100	−94	−30	−27	−17
p Value	<0.001	>0.05	<0.02	<0.02	<0.001	<0.001	<0.001	<0.001	0.01-0.02

ing the preinhalation and postinhalation rates of rise in the brachial arterial pressure pulse the positive directional change (16 per cent) was not significant ($p > 0.05$) However the use of fluid filled connecting tubing may have influenced the accuracy of this determination of the instantaneous rate of change in pressure [39] The frequent appearance of an anacrotic water hammer [36] (an obvious spike occurring at the top of the anacrotic limb) (Fig 3) and the earlier occurrence of the systolic peak suggested a more rapid rate of rise in the brachial pulse The decreased duration of left ventricular contraction (interval between mitral and aortic valve closures)[21] could not be explained by the decrement in isometric contraction (Fig 4) and hence must have in part reflected a decline in ejection time A decrease in the duration of left ventricular ejection without a decrease in stroke volume implies a more rapid rate of ejection In addition amyl nitrite consistently caused a shortening of the appearance time and mean recirculation time of the injected indicator reflecting a more rapid rate of circulation

During the inhalation of amyl nitrite the amplitude of the dicrotic wave of the brachial pulse decreased and the dicrotic notch assumed a progressively lower position finally merging in most instances with the nadir of the diastolic trough[4] (Figs 2 and 3) Although the dicrotic wave has generally been attributed to rebound of the column of arterial blood against the closed aortic valve other studies suggest that peripheral factors may contribute materially to its formation [40] A decline in the level of the dicrotic notch has been observed as a response to vasodilatation The peripheral runoff of blood was believed to exceed the amount being ejected by the heart in mid-systole thus allowing the arterial pressure to fall well in advance of the dicrotic incisura It is of interest in this regard that nitroglycerin[4] and amyl nitrite which decrease peripheral vascular resistance lower the level of the dicrotic notch whereas pressor amines which increase peripheral vascular resistance elevate the level of the dicrotic notch

Auscultatory and phonocardiographic inferences As amyl nitrite causes an increase in cardiac output and in the rate of left ventricular ejection and a decrease in circulation time and systolic arterial pressure the murmur of aortic stenosis should amplify under the influence of this drug [17] On the other hand as resistance to left ventricular discharge declines and as the rate of ejection increases the murmur of mitral incompetence should soften [14,15,17] In like fashion a fall in systemic systolic pressure should reduce the intensity of the murmur of small ventricular septal defect [4] and a fall in systemic diastolic pressure should reduce the intensity of the murmur of aortic incompetence.[41] Augmented flow into the left atrium together with a more rapid circulatory rate and a decrease in the diastolic filling period should cause the murmur of mitral stenosis to become amplified [42] On the other hand, the decreased intensity of the murmur of aortic incompetence[43] is associated with a parallel decrease in the Austin Flint murmur [44] permitting separation of the latter from the murmur of mitral stenosis which regularly behaves in an opposite fashion.[2,3] In tetralogy of Fallot a fall in systemic resistance should cause the right ventricle to increase its flow into the aorta and to decrease its flow into the pulmonary artery resulting in a decline in intensity of the pulmonic systolic murmur [45]

Summary

In spite of the increasing use of amyl nitrite in the auscultatory phonocardiographic and hemodynamic diagnosis of heart disease data on its circulatory effects in normal man were incomplete Because of this observations were made on 25 normal young subjects under conditions similar to those employed when the drug is used as a diagnostic agent in the assessment of the cardiac patient. The studies indicate that amyl nitrite causes (1) a decrease in systemic arterial pressure vascular resistance, stroke work circulation time level of the dicrotic notch amplitude of the dicrotic wave and duration of left ventricular contraction ejection and diastolic filling period (2) an increase in heart rate cardiac index and ejection velocity and (3) no change in stroke volume or minute work. Phonocardiographic implications are briefly discussed

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Autopsy study of heart disease in the Philippines General Hospital

Based on a review of 6,000 consecutive cases

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The Philippines General Hospital is located in the heart of Manila and functions as a teaching hospital for the College of Medicine of the University of the Philippines and as a general service hospital It has a capacity of 960 beds, with a yearly hospital admission of well over 35 000 patients 90 per cent of whom are charity patients The main bulk of the patients are from Manila and its suburbs (about 80 per cent) and the rest come from all over the Philippines. The majority of these patients are from the social level which comprises the major segment of the Philippine population The autopsy rate averages about 75 per cent per annum Thus, an unselective study of its autopsy material is highly representative of the total mortality of the hospital population and presumably a fairly good sample of the mortality of the Philippine population

The present study was undertaken in order to determine what cardiac diseases are found here the relative frequency of cardiac deaths according to specific causes and how the different cardiac diseases are characterized especially in terms of age and sex factors.

Materials and methods

A review of 6 000 consecutive autopsies (stillbirths excluded) was made in the Department of Pathology of the Philippines General Hospital from 1953 to 1960 All cases which showed cardiopathies were studied according to the nature of the cardiac pathology as a cause of death and its frequency distribution according to age and sex groups. Comparative analysis were made between the major cardiopathies.

Results

Table I shows the different cardiac pathologies found in the series and the number of cases of each cardiopathy seen according to age and sex groups. Of the 6 000 necropsies a total of 1 240 cases (20 7 per cent of the series) showed cardiac pathology The percentile distribution of these cases of cardiopathies in relation to the total number of deaths per age group corresponds to the unshaded area in the

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Table I Cardiac pathologies found and the number of cases of each cardiopathy according to age and sex groups

Cardiac lesions present		Total ages	Age groups (in years)							
			0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–Over
All cardiopathies	T	1 240	115	93	96	100	194	257	218	167
	M	715	59	40	49	49	112	166	136	104
	F	525	56	53	47	51	[illegible]	91	82	63
CHD	T	67	60	2	3	2	0	0	0	0
	M	36	30	1	3	2	0	0	0	0
	F	31	30	1	0	0	0	0	0	0
RHD	T	291	21	76	65	43	48	21	13	4
	M	125	12	30	29	15	20	12	5	2
	F	166	9	46	36	28	28	9	8	2
PHHD	T	65	1	6	6	15	23	12	2	0
	M	[illegible]	0	5	1	8	16	10	2	0
	F	23	1	1	5	7	7	2	0	0
HCA	T	237	0	0	2	11	59	80	51	34
	M	160	0	0	1	7	40	60	35	17
	F	77	0	0	1	4	19	20	16	17
PCA	T	436	0	0	2	7	41	117	143	126
	M	276	0	0	1	5	23	72	91	84
	F	160	0	0	1	2	18	45	52	42
CP	T	71	6	4	7	11	10	24	7	2
	M	31	3	1	4	6	4	10	2	1
	F	40	3	3	3	5	[illegible]	14	5	1
IHD	T	43	21	4	5	4	5	1	2	1
	M	25	11	2	4	3	3	1	1	0
	F	18	10	2	1	1	2	0	1	1
SYHD	T	12	0	0	4	3	4	1	0	0
	M	11	0	0	4	2	4	1	0	0
	F	1	0	0	0	1	0	0	0	0
BBHD	T	8	5	0	0	3	0	0	0	0
	M	3	3	0	0	0	0	0	0	0
	F	5	2	0	0	3	0	0	0	0
THD	T	4	0	0	1	0	2	1	0	0
	M	1	0	0	1	0	0	0	0	0
	F	3	0	0	0	0	2	1	0	0
Misc	T	6	1	1	1	1	2	0	0	0
	M	5	0	1	1	1	2	0	0	0
	F	1	1	0	0	0	0	0	0	0
All cases	T	6 000	3 419	321	451	400	469	462	290	190
	M	3 262	1 919	155	188	161	260	282	180	119
	F	2 738	1 500	166	263	239	209	180	110	71

CHD: Congenital heart defects. RHD: Rheumatic heart disease. PHHD: Pure hypertensive heart disease. HCA: Coronary arteriosclerosis associated with hypertension. PCA: Coronary arteriosclerosis without hypertension. CP: Cor pulmonale. IHD: Infectious heart disease. SYHD: Syphilitic heart disease. BBHD: Beriberi heart disease. THD: Thyrotoxic heart disease. Misc.: Miscellaneous heart diseases. T: Total. M: Male. F: Female.

Table II Percentile distribution of the different cardiopathies as a cause of death in the different age groups

0–10 years		
CHD		0.8
RHD		0.6
Others		0.4
Total		1.8

11–20 years		
RHD		23.7
CP		1.3%
PHHD		0.[illegible]
Others		0.9
Total		26.8

21–30 years		
RHD		13.1
CP		1.1
IHD		1.1
SYHD		0.9%
Others		0.9%
Total		17.1

31–40 years		
RHD		9.2
CP		2.7
CAHD		1.6
PCA	0.8	
HCA	0.8	
Others		2.0%
Total		15.5

41–50 years		
RHD		6.7
CAHD		4.3%
PCA	2.8%	
HCA	1.5%	
CP		1.7%
Others		2.6%
Total		17.3%

51–60 years		
CAHD		6.7%
HCA	4.1	
PCA	2.6%	
CP		4.8%
RHD		3.[illegible]%
Others		0.8%
Total		16.0%

61–70 years		
CAHD		8.6%
PCA	5.2	
HCA	3.4%	
CP		2.4%
RHD		1.0%
Total		12.0%

71–Over years		
CAHD		13.2%
PCA	9.5%	
HCA	3.7%	
Others		1.0%
Total		14.2

CAHD Coronary arteriosclerotic heart disease. For other abbreviations see footnotes Table I.

upper graph of Fig. 1 (*Cardiacs*). There were 504 cases of cardiac death, i.e. the cardiac lesions were the specific cause of death accounting for 8.4 per cent of the total series. The percentile distribution of these cardiac deaths in relation to the total number of deaths per age group corresponds to the shaded area in the upper graph of Fig. 1. A breakdown of the different cardiopathies which caused these cardiac deaths in each age group is shown in Table II. Fig. 2 shows the percentile distribution of all the cardiac deaths according to specific causes. Fig. 3 shows the distribution of the cardiac lesions according to sex.

Congenital heart defects were present in 67 cases (1.12 per cent of the series). The distribution of these cases according to age groups may be seen in Fig. 4 (*unshaded area*). In this same figure, the shaded area corresponds to deaths caused by these lesions in the different age groups. Congenital heart defects were the cause of death in 0.5 per cent of the whole series and accounted for [illegible].4 per cent of all cardiac deaths.

No significant sex ratio difference was noted.

The types of congenital defects found are shown in Table III.

Rheumatic heart disease was found in 291 cases (4.85 per cent of the series). Fig. 5 shows the distribution of these cases and the deaths due to this disease according to age groups. The average age at death was 28.5 years. The relationship of rheumatic deaths to total deaths in the different age groups is seen in Fig. 1 (*Rheumatic*). It can be noted that the greatest number of

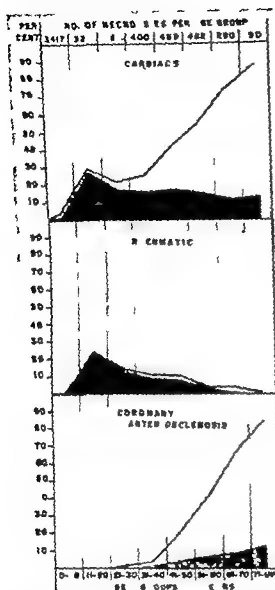


Fig. 2. Upper graph (*Cardiac*) shows the percentile distribution of cardiopathies (*unshaded area*) and cardiac deaths (*shaded area*) according to age groups. Middle graph (*Rheumatic*) shows the percentile distribution of rheumatic cases (*unshaded area*) and rheumatic deaths (*shaded area*). Lower graph (*coronary arteriosclerosis*) shows the percentile distribution of cases of coronary arteriosclerosis (*unshaded area*) and deaths (*shaded area*) secondary to this lesion.

rheumatic deaths occurred in patients between the ages of 11 and 20 years (76 cases) in which age range rheumatic heart disease also accounted for 23.7 per cent of all deaths or roughly 1 of every 4 necropsies. In the whole series it was responsible for death in 254 cases, or 4.25 per cent and was the major cause of all cardiac deaths (50.1 per cent).

Sex ratio showed a significant preponderance ($p < .0001$) of females over males (about 3:2).

Signs of acute carditis were found in about 20 per cent of all rheumatic hearts in patients under 20 years of age and in less than 5 per cent of hearts in patients over this age.

Table IV shows the percentile distribution of the different valvular lesions found.

Pure hypertensive heart disease was found in 65 cases (1.08 per cent of the series)

Table III. Types of congenital defects and the number of cases of each defect

Type of congenital defect	Number of cases
Isolated defects	
Interventricular septal defect	16
Patent ductus arteriosus	10
Interatrial septal defect	5
Endocardial fibroelastosis	3
Other	4
Total	38
Multiple defects	
Interventricular septal defect with pulmonic stenosis	14
Transposition of the great vessels	5
Interventricular septal defect with interatrial septal defect	3
Other	7
Total	29

Table IV. Percentile distribution of the valvular lesions found in cases of rheumatic heart disease

Valvular involvement	Per cent
Pure mitral	41.8
Mitral-aortic	23.5
Mitral-aortic-tricuspid	15.4
Mitral-tricuspid	8.7
Pure aortic	6.2
Mitral-aortic-tricuspid-pulmonic	1.8
Mitral-aortic-pulmonic	1.8
Mitral-tricuspid-pulmonic	1.4

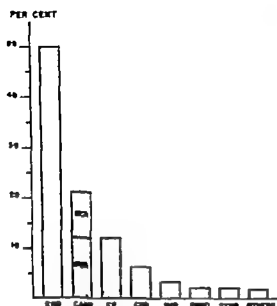


Fig. 2. Percentile distribution of cardiac death according to specific causes. See footnote to Table I for key to abbreviations.

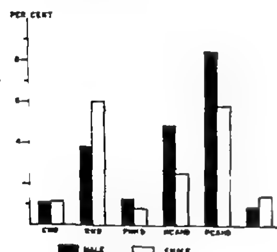


Fig. 3. Percentile distribution of cardiopathies according to sex. See footnote to Table I for key to abbreviations.

The distribution of these cases and the cardiac deaths associated with this disease according to age groups is seen in Fig. 6. Pure hypertensive heart disease was the cause of death in only 0.18 per cent of the whole series (11 cases) and accounted for 2.18 per cent of all cardiac deaths. The majority of deaths which resulted from this disease were due to extracardiac causes (kidney failure, cerebrovascular complications, etc.)

Although there was a preponderance of males over females (1.29 versus 0.84 per cent) the difference was not statistically significant in this series (p = .09).

Coronary arteriosclerosis was present in 673 cases (11.2 per cent of the series). In 237 of these there was associated hypertension (HCA) and in the other 436 coronary arteriosclerosis was an isolated cardiac lesion (PCA). Figs. 7 and 8 show respectively the distribution of cases of HCA and PCA (including deaths attributable to these lesions) according to age groups. The relationship of coronary arteriosclerosis to total deaths per age group may be seen in Fig. 1 (*Coronary Arteriosclerosis*). An almost perfect linear relationship is seen between the distribution of this lesion (in relation to total deaths per age group) and advancing age beyond 40 years. *From this graph it may be noted that with* increasing age there is a progressive deviation between the frequency distribution of cases of coronary arteriosclerosis and cardiac deaths secondary to this lesion. In the 31 to 40-year age group the ratio is 3:1, in the 41 to 50-year age group it is 5:1, in the 51 to 60-year age group it is 6.4:1, in the 61 to 70-year age group it is 7.8:1, and in the 71 year-and-over age group it is 6.4:1.

Coronary arteriosclerosis was the cause of death in 1.79 per cent (107 cases) of the whole series and accounted for 21.3 per cent of all cardiac deaths. Table V shows

Table V. Causes of cardiac death in cases of coronary arteriosclerosis and the number of deaths due to each cause

Type of cardiac lesion	*Number of death*
Coronary arteriosclerosis with hypertension	
Acute myocardial infarction	16
Congestive heart failure	27
Total	43
Pure coronary arteriosclerosis	
Acute myocardial infarction	43
Congestive heart failure	18
Total	61

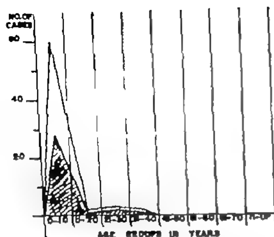


Fig. 4 Frequency distribution of congenital heart defects according to age groups. Unshaded area corresponds to the number of cases, and shaded area to the number of deaths.

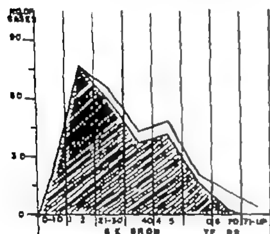


Fig. 5 Frequency distribution of rheumatic heart disease according to age groups. Unshaded area corresponds to the number of cases, and shaded area to the number of deaths.

the specific causes of cardiac death in cases of coronary arteriosclerosis, and indicates that acute myocardial infarction was mainly responsible in cases of pure coronary arteriosclerosis. A greater majority of patients with coronary arteriosclerosis died of cerebrovascular accidents (especially in those cases associated with hypertension)

Sex ratio showed that there was a preponderance of males over females in both HCA (roughly 2 1) and PCA (roughly 3.2) and the differences are statistically significant (p < 0002 in both)

Cor pulmonale (heart-lung disease) was found in 71 cases (1 2 per cent of the series) and was the cause of death in 62 (1 03 per cent of the series) The distribution of these cases and the deaths due to this disease according to age groups is seen in Fig 9 It can be noted that it is found in all age groups the greatest number of cases was found in the 51 to 60-year age group. As with rheumatic heart disease, this lesion when found at autopsy is usually the cause of death.

No significant sex ratio difference was established in this study

The primary lung diseases found in the order of their frequency were pulmonary tuberculosis, chronic bronchial asthma, bronchiectasis, and other nonspecific diseases.

Infectious heart disease was present in 43 cases (0 7 per cent of the series) and was the cause of death in 17 (0.3 per cent of the series) Distribution was in all age groups with about half of the cases (21) found in age group 0-10 years.

The various infectious heart diseases found were pericarditis (70 per cent) nonspecific myocarditis (25 per cent) and acute endocarditis (5 per cent)

Syphilitic heart disease was found in 12 cases 11 of these cases were in males. All cases were found in the age range between 20 and 60 years. This lesion was the cause of death in 11 of the 12 cases.

Beriberi heart disease was found in 8

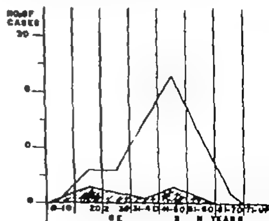


Fig. 6 Frequency distribution of pure hypertensive heart disease according to age groups. Unshaded area corresponds to the number of cases, and shaded area to the number of deaths.

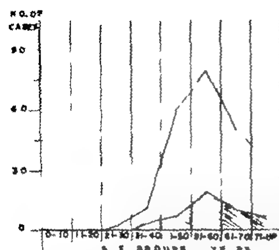


Fig. 7 Frequency distribution of coronary arteriosclerosis associated with hypertension according to age groups. Unshaded area corresponds to the number of cases, and shaded area to the number of deaths.

cases and was the cause of death in 3. Distribution of these cases was in the age groups below 40 years.

Thyrotoxic heart disease was found in 4 cases and was the cause of death in 3. Of the 4 cases, 3 were in women.

Other heart diseases found were leukemic infiltrations, periarteritis nodosa, marasmic heart disease, myxoma of the left atrium, and nonspecific (n 2).

Comments

The results of this study show clearly that rheumatic heart disease and coronary arteriosclerosis were mainly responsible for the frequency distribution of cardiac cases and cardiac deaths in the different age groups (see Fig. 1).

Rheumatic heart disease apparently holds the greatest importance. It not only accounted for half of all cardiac deaths but was responsible for practically 1 of every 4 deaths in the 11 to 20-year age group. At present, the actual incidence of this disease in the Philippines is not known. However, a survey of hospital admissions reported in 1955 by Almurung and associates showed that rheumatic heart disease was the leading etiological type of all cardiac diseases. These observations are contrary to the belief that this disease is found essentially in temperate climates. Further evidence in this regard is its reportedly high incidence in Mexico,[2] Taiwan,[3] and India.[4] The large number of deaths which occur in the younger age groups in this study suggests a rapid progressively fatal course of the disease here. A similar finding has been reported by Sta. Ana and associates[5] in their 12-year pathologic survey of 2,375 cases from another general hospital here in Manila. Certainly, a reappraisal of the different factors currently believed to be associated with this disease is warranted—based perhaps on a larger geographical scale.

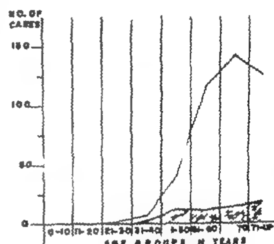


Fig. 8 Frequency distribution of coronary arteriosclerosis without hypertension according to age groups. Unshaded area corresponds to the number of cases, and shaded area to the number of deaths.

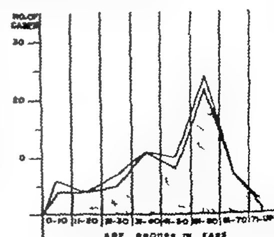


Fig. 9 Frequency distribution of cor pulmonale according to age groups. Unshaded area corresponds to the number of cases, and shaded area to the number of deaths.

Coronary arteriosclerosis had the greatest frequency of all cardiopathies, with a percentile distribution that showed a linear relationship with advancing age above 40 years. However in the case of this cardiac pathology a progressive deviation of the ratio between the number of cases and the number of cardiac deaths was observed with advancing age groups. The greater number of deaths due to this lesion were extracardiac in cause predominantly cerebrovascular in origin This confirms an earlier observation by Barrera [6] who found a preponderance of cerebrovascular over cardiac causes of death in cases of arteriosclerosis.

Hypertensive heart disease if taken as a separate cardiac entity would correspond to what has been labeled as pure hypertensive heart disease and coronary arteriosclerosis associated with hypertension This would comprise a total of 302 cases in this series and would be responsible for 57 cardiac deaths.

Cases of cor pulmonale comprised a small segment of the total number of cardiopathies (71 out of 1,240 cases) However it ranked third closely following coronary arteriosclerosis as a cause of cardiac death As with rheumatic heart disease cor pulmonale is usually the cause of death when found at autopsy

Summary and conclusions

Six thousand consecutive necropsies were reviewed in the Department of Pathology of the University of the Philippines–Philippines General Hospital Medical Center from 1953 to 1960 Cardiac lesions were found in 1,240 cases, and in 504 of these the cardiac pathology was the direct cause of death.

Rheumatic heart disease was found in 4.85 per cent of the series and was the cause of death in 4 25 per cent It was the major cause of cardiac death (50 1 per cent) as well as a major cause of death in the age group 11 20 years. The average age at death was 28.5 years. Sex ratio showed a preponderance of females over males (3.2)

Coronary arteriosclerosis was present in 11 2 per cent of the series, and had the highest frequency of all cardiopathies. However it was responsible for only 1 79 per cent of all deaths and 21.3 per cent of all cardiac deaths. Percentile distribution of this cardiac lesion showed a linear relationship with advancing age above 40 years. Sex ratio showed a preponderance of males over females (2 1 when associated with hypertension and 3 2 in the absence of hypertension)

Cor pulmonale was present in 1.2 per cent of the series and was the cause of death in 1 03 per cent It accounted for 12.3 per cent of all cardiac deaths.

Congenital heart disease was found in 1 12 per cent of the series and was the cause of death in 0 5 per cent (6 4 per cent of all cardiac deaths)

Infectious heart disease was present in 0 7 per cent of the series and was the cause of death in 0 3 per cent (3 4 per cent of all cardiac deaths)

Pure hypertensive heart disease was found in 1 08 per cent of the series and was the direct cause of death in 0 18 per cent (2 2 per cent of all cardiac deaths)

Syphilitic heart disease was present in 12 cases (11 males) and was the cause of death in 11 (2.2 per cent of all cardiac deaths)

Other heart diseases found were beriberi heart disease thyrotoxic heart disease, leukemic infiltration of the left ventricle, periarteritis nodosa marantic heart disease myxoma of the left atrium and nonspecific type (2 cases)

We thank Dr Paulo C Campos, Head Dept. of Internal Medicine and Dr Benjamin Canlas Head, Dept. of Pathology College of Medicine, University of the Philippines, for encouragement suggestions, and review of this article.

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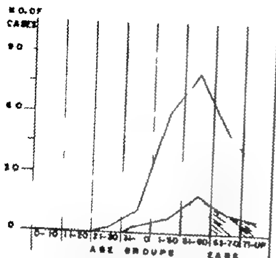


Fig. 7. Frequency distributio of coronary arterio-sclerosis associated with hypertension according t ge groups. U shaded rea corresponds t the n m ber of cases nd shaded re t the number of de hs.

cases ar d was the cause of death in 3. Distribution of these cases was the age groups below 40 years.

Thyrotoxic heart disease was found in 4 cases a d was the cause of death in 3. Of the 4 cases, 3 were women.

Other heart diseases found were leukemic infiltr tions periarteritis nodosa marantic heart disease a noma of the left atrium d nonspecific (n 2).

Comments

The results of this study show clearly that rheu natic heart disease and coronary arteriosclerosis were mainly responsible for the frequency distribution of cardiac cases and cardiac deaths in the different age groups (see Fig. 1).

Rheumatic heart d sease apparently holds the greatest importance. It not only accounted for half of all cardiac deaths but was responsible for practically 1 of every 4 deaths in the 11 to 20- ear age group. At present the actual incidence of this disease in the Philippines is not known. However a survey of hospital admissions reported in 1955 by Al murung and associates[1] showed that rheumatic heart disease was the leading etiological type of all cardiac diseases. These observations are contrary to the belief that this disease is found essentially in temperate climates. Further evidence in this regard is its reportedly high incidence in Mexico,[2] Taiwan[3] and India.[4] The large number of deaths which occur in the younger age groups in this study suggests a rapid progressively fatal course of the disease here. A similar finding has been reported by Sta. Ana and associates[5] in their 12 year pathologic survey of 2,375 cases from another general hospital here in Manila. Certainly a reappraisal of the different factors currently believed to be associated with this disease is warranted—based perhaps, on a larger geographical scale.

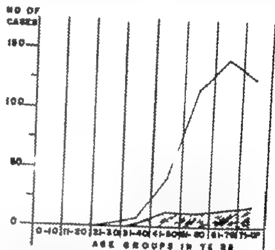


Fig. 8. Frequency distribution of coronary rterio-sclerosis w thout hypertension according to age groups. Unshaded area corresponds t the number of cases, nd shaded area t the number of deaths.

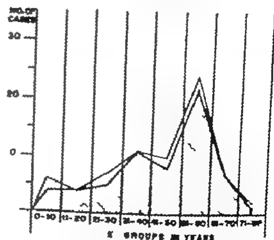


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side of the heart disclosed a large ventricular septal defect. This was located anterosuperiorly to the crista supraventricularis (Fig. 2, *upper left and right*). The defect had no superior margin since it was straddled by the pulmonary trunk, which took origin from both ventricles, principally from the left. The aorta arose entirely from the right basal aspect of the right ventricle and was separated from the ventricular septal defect and from the pulmonary valve by the parietal limb of the crista supraventricularis. As a result of this anatomic situation there was an element of subaortic obstruction. Since the ventricular septal defect lay anteriorly the tricuspid valve did not enter into direct contact with the defect. The papillary muscle of the conus, as it inserted into the septal limb of the crista supraventricularis, formed part of the lower edge of the defect.

Viewed from the left side the ventricular septal defect was seen at the junction of the anterior wall of the left ventricle and the ventricular septum (Fig. 2, *lower left and right*). Muscular tissue separated the mitral valve from the defect.

In complete transposition of the great vessels the pulmonary trunk arises entirely from the left ventricle. In the condition discussed here, the major part of the pulmonary trunk exhibited a similar origin as well as continuity of the anterior leaflet of the mitral valve with pulmonary valvular tissue. In contrast to the arrangement in complete transposition, however, the pulmonary trunk straddled the ventricular septal defect and about one fifth of its circumference was anchored to the anterior wall of the right ventricular base.

The aortic and pulmonary valves were each equipped with semilunar cusps. The two valves were located at the same horizontal body plane. No atrioventricular valvular tissue joined the aortic valve.

Both ventricles were dilated and hypertrophied and each showed the anatomic characteristics of the normal ventricle of the particular side. A valvular competent patent foramen ovale was present. The atrioventricular valves were normal and the systemic and pulmonary veins terminated in the proper atrial chambers.

An obstructive malformation of the aortic arch was observed in each case. In Case 1 the obstruction was represented by a zone of tubular hypoplasia of the aortic arch between the origins of the left common carotid and the left subclavian arteries (Fig. 1, *right*). In Case 2 a zone of classic aortic coarctation beyond the left subclavian artery had been removed surgically. The ductus arteriosus was obliterated in each case.



Fig. 1. Right ventricular aorta and biventricular pulmonary trunk. *Left*. Case 1. The ascending aorta (*A*) lies to the right of the dilated pulmonary trunk (*P*). In contrast to the normal, the aorta does not exhibit the leftward curvature behind the pulmonary trunk. *Right*. Case 2. Anterior view of the great vessels. Features like those in Case 1 (*left*). In addition, there is tubular hypoplasia of the aortic arch (*point of arrow*) between the left common carotid and left subclavian arteries.

Clinical features

The clinical data of the 2 cases observed will be presented in composite form.

Mild cyanosis was observed at birth in Case 1 and in the early neonatal period in Case 2. Although no murmurs were heard at birth, a murmur was detected during the newborn period. Congestive cardiac failure developed at 6 weeks of age in Case 1 and 2 weeks of age in Case 2.

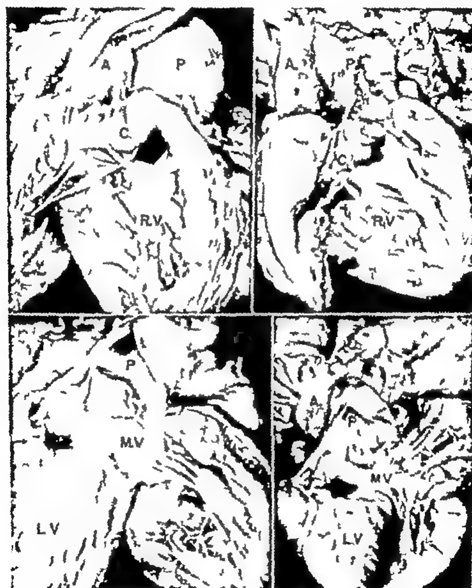


Fig. 2. Right ventricular aorta and biventricular pulmonary trunk. *Relationships of the two great vessels to the ventricles.* *Upper left,* Case 1. The aorta (*A*) arises entirely from the right ventricle (*RV*). The ventricular septal defect is anterior to the crista supraventricularis (*C*). The pulmonary trunk (*P*) arises partially from the right ventricle above the defect. *Upper right,* Case 2. The interrelationships between the great vessels and the right ventricle are like those in Case 1 (*upper left*). The probe lies in the relatively narrow subaortic compartment. *Lower left,* Case 1. From the left side, it is apparent that the pulmonary trunk (*P*) arises predominantly from the left ventricle (*LV*). The anterior leaflet of the mitral valve (*MV*) is continuous with pulmonary valvular tissue. *Lower right,* Case 2. Interior of the left ventricle (*LV*). The interrelationships of the pulmonary trunk (*P*) and mitral valve (*MV*) are like those in Case 1 (*lower left*). *A,* Exterior of ascending aorta.

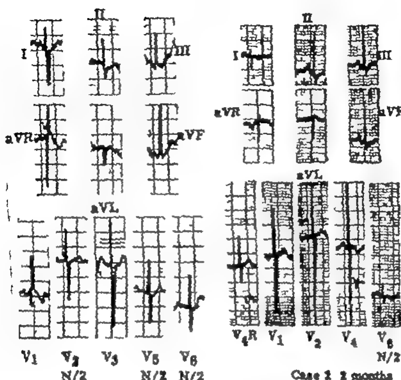


Fig. 3. Electrocardiograms in the 2 reported cases. *Left*, Case 1. Biventricular hypertrophy. Note the tall biphasic RS complexes in precordial Leads V_2–V_5. *Right*, Case 2. Biventricular hypertrophy. Note the tall biphasic RS complexes in all precordial leads. N/2 = one-half standardization.

From the neonatal period each patient experienced recurrent respiratory infections and poor gain in weight.

Physical examination showed each patient to be small, thin, and poorly developed.

Determinations of blood pressure by the flush method gave normal results in Case 1. In Case 2, the pressure was 80 mm. Hg in an arm and 40 mm. Hg in a leg. (Subsequently, a coarctation of the aorta was resected.)

Cardiomegaly was evident in both patients. In Case 1, a localized systolic thrill was felt at the fourth left intercostal space adjacent to the left sternal border. A thrill was not felt in Case 2. In each, a loud Grade 3 to 4 (6) holosystolic murmur was heard maximally along the lower left sternal border, but was also prominent over the entire precordium and back. A soft, short diastolic murmur was heard at the apex in Case 1; some observers reported a diastolic murmur at the same area in Case 2. The second cardiac sound at the pulmonary area was narrowly split in Case 1 and appeared to be loud and single in Case 2.

Electrocardiographic findings. Electrocardiographic abnormalities were present in both cases (Fig. 3). No conduction disturbances were apparent, and the P waves indicated normal atrial size in each. Biventricular hypertrophy was indicated in both cases.

Radiologic features. Radiologic studies had been done only in Case 2. The thoracic roentgenograms in Case 2 showed pronounced cardiac enlargement (Fig. 4). Both ventricles appeared to be enlarged and the pulmonary vascularity was moderately increased. Left atrial enlargement was indicated by a barium-filled esophagus deviated posteriorly and to the right (Fig. 4). The superior mediastinum was relatively narrow, and neither the aorta nor pulmonary trunk was identifiable.

In Case 2, injection of the contrast medium into the right ventricle showed dense



Fig 4 Thoracic roentgenograms in Case 2 *Left.* Anteroposterior view Pronounced cardiomegaly and increased pulmonary vascularity The esophagus (with barium) is deviated t the right. *R ght* Lateral iew Posterior deviation of the esophagus owing t an enlarged left trium.

opacification of the aorta (Fig 5) In the lateral view the ascending aorta failed to show the usual posterior turn of the origin of the vessels (Fig 5 *right*)

The origin of the aorta was in line with the outflow tract of the right ventricle (Fig 5) In the same view the anterior and posterior borders of the dilated pul monary trunk extended beyond the cor respond ng borders of the ascending aorta. The aortic valve was unusually high and was observed lying at the same horizontal level as the pulmonary valve. After selec ti e right ventriculography the opacifica tion of the aorta was of a greater degree than that of the pulmonary trunk (Fig 5) Tubular hypoplasia and coarctation of the aorta was additionally observed (Fig 5 *right*)

Cardiac catheterization had not been performed in either of the 2 cases.

The condition could be given the de scripti e name of *right ventricular aorta and biventricular pulmonary trunk* This would be in contrast to the Taussig Bing com plex which is a form of origin of both vessels from the right ventricle.

Comment

The condition here reported (which re sembled the Taussig Bing malformation in some ways and complete transposition of the great vessels, in others) is rare This fact is exemplified by observing these 2 cases in a pathologic collection which contained 60 cases of complete transposi tion and 4 cases of Taussig Bing complex. Keith and associates[4] have described a condition termed complete transposition of the great vessels with overriding pul monary artery The condition reported herein differs from the cases described by Keith in the following manner (1) the ventricular septal defect in our cases was more anteriorly placed in the ventricular septum and (2) the great vessels in our cases were in near normal position whereas the great vessels in Keith s cases were identical with those of complete transposi tion

With respect to the Taussig Bing mal formation our 2 cases differed in two re spects. In the Taussig Bing malformation the pulmonary trunk, although arising near the ventricular septal defect arises entirely from the right ventricle. In our cases the origin of the pulmonary trunk straddled the ventricular septal defect and arose from *both* ventricles principally the left. Secondly in the Taussig Bing mal formation the mitral valve does not make continuity with either semilunar valve. In our cases, elements of the mitral and pul monary valves were continuous. The latter arrangement is also present in complete transposition yet in complete transposition the pulmonary trunk arises entirely from the left ventricle. Therefore, the biven

tricular origin of the pulmonary trunk in our cases would represent an important difference from the situation in complete transposition.

It would be helpful if clinical, electrocardiographic, and radiologic studies could provide a means of distinguishing this condition from the more common conditions of Taussig-Bing malformation and complete transposition of the great vessels.

From a functional viewpoint these cases seem to have a more fundamental resemblance to the Taussig-Bing malformation. Early-appearing cyanosis and congestive cardiac failure associated with loud murmurs, however, are commonly observed among patients with complete transposition of the great vessels in whom large communications between the two circulations are present.

Electrocardiographically there was one finding which in our experience is uncommonly observed among patients with Taussig-Bing malformation or complete transposition. This was a wide-open QRS loop directed anteriorly, represented by tall biphasic RS complexes in either the majority or all of the conventional precordial leads. The experiences in 2 patients, however, hardly yield sufficient evidence to justify firm judgments.

In the one case with angiocardiographic studies, typical features of the Taussig-Bing malformation were considered to be present. The angiocardiographic similarities included the relationship of the two great vessels to themselves and the relationship of the pulmonary trunk to the anteriorly situated ventricular septal defect. These features were (1) the anterior aspect of the pulmonary trunk situated partly anteriorly to the ascending aorta, (2) absence of the normal left inward curvature of the beginning of the ascending aorta, (3) the semilunar valves in the same horizontal body plane, (4) the pulmonary trunk less densely opacified than the ascending aorta in the right ventriculogram, and (5) the presence of obstructive malformations of the aortic arch. Thus, the angiocardiographic features were like those in the Taussig-Bing malformation, although fundamental anatomic differences between the two conditions were present.



Fig. 5. Selective angiocardiograms from the right ventricle (*R.V.*) in Case 2. *Left*. Anteroposterior view. The ascending aorta (*A.*) and pulmonary trunk (*P.T.*) are opacified simultaneously. The dilated pulmonary trunk is less densely opacified than is the ascending aorta. *Right*. Lateral view. The ascending aorta (*A.*) is situated more anterior than normally, is lacking the normal curvature toward the left ventricle, and is in direct line with the outflow tract of the right ventricle (*R.V.*). The anterior and posterior borders of the dilated pulmonary trunk (*P.T.*) extend beyond the corresponding borders of the ascending aorta (*A.*). The arrow points toward the site of coarctation of the aorta. The patent ductus arteriosus is also seen below the site of coarctation.

The so-called Taussig Bing malformation among congenital cardiac anomalies is considered to be so complex that no surgical procedure for its correction has yet been devised. However surgical procedures for correction of the entity of complete transposition have been devised. It would seem that by closing the anteriorly situated ventricular septal defect in the condition herein reported the functional as well as the anatomic results would be the same as those in a case of complete transposition. From this point the problem in surgical correction would be as in complete transposition.

Summary

Two cases are described in which the aorta arises from the right ventricle while the pulmonary trunk arises above a ventricular septal defect from both ventricles, mainly the left.

Anatomically the condition herein called *right ventricular aorta and biventricular pulmonary trunk* lies between classic complete transposition of the great vessels on one hand and the Taussig Bing complex, on the other.

Distinguishing points are that in the Taussig Bing malformation the pulmonary trunk which arises near a ventricular septal defect takes its origin entirely from the right ventricle. In the cases here described the biventricular pulmonary trunk straddles a ventricular septal defect and arises mainly from the left ventricle. Continuity between elements of the mitral and pulmonary valves which is a characteristic of the cases here described is not exhibited by the Taussig Bing malformation. Origin of the pulmonary trunk from both ventricles is a major difference from the origin of that vessel in complete transposition. In the latter malformation the pulmonary trunk arises entirely from the left ventricle.

The fundamental functional derangements as judged by clinical examination and angiography are more like those of the Taussig Bing complex than those of complete transposition.

From a surgical point of view problems in correction seem to be more closely allied to those of complete transposition than to those of the Taussig Bing complex.

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Rotational cinefluorography of the heart and lungs

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Motion of the heart and lungs is readily apparent in cinefluorograms of the chest which often disclose information that is not apparent in standard roentgenograms. In routine fluoroscopy rotation of the patient is essential in localizing the pulmonary lesions and in determining the size of cardiac chambers.

Rotation of a subject in a cinefluoroscopic field was first mentioned in 1953 by Weinberg Watson and Gramiak. Rotation of the patient through 1 to 6 inches was found to produce a stereoscopic effect. In 1956, Weinberg Watson and Ramsey[4] again mentioned rotation but no description of the method of rotation or examples of films were given. In 1959 Winter and Lehman[3] described a method for the rotation of dogs through 360 degrees in a plastic crib during cinefluorography but the mode of rotation was too cumbersome for adaptation to human beings. They did however foresee far reaching possibilities for improvements in roentgen diagnoses as a result of the use of the rotational principle.

A practical method for the rotation of a patient through a full circle in a cinefluorographic field designed for clinical use in the diagnosis of cardiac and pulmonary disease is described in the present paper

Method

The patient is seated on a specially constructed chair in front of a cinefluorographic unit (Fig 1) The base of the chair assembly is electrically powered and rotates through a full circle in 5 seconds. The height of the chair is adjustable according to the size of the patient The patient stabilizes himself by grasping an overhead bar which rotates as the chair turns (Fig 2)

For routine cinefluoroscopic studies of the heart and lung fields, the patient swallows barium inspires fully and holds his breath He is then rotated to his right while a 7-second cinefluorogram is made Bronchographic cinefluorography is accomplished in a similar manner except that no barium swallow is given Films must be made as soon after administration of the bronchial contrast medium as possible

For studies of the pulmonary vasculature an injection catheter is first placed in the superior vena cava. The patient is then seated on the rotating chair and the catheter is connected via a special connector (Fig 2) to a pneumatic injector

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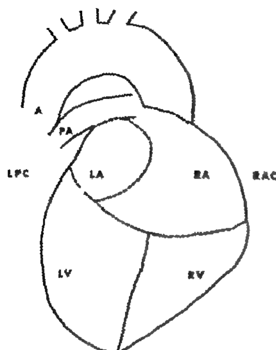


Fig 4 Diagram of cardiac borders in the right posterior oblique position. *A* Aorta *PA* Pulmonary artery *LA* Left atrium *RA* Right atrium. *LV* Left ventricle *RV* Right ventricle *LPC* Left posterior chest *RAC* Right anterior chest

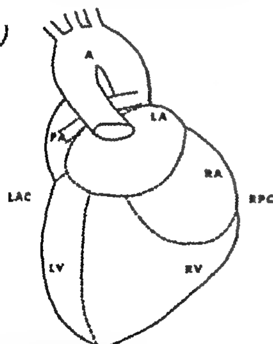


Fig 5 Diagram of cardiac borders in the left posterior oblique position. See Fig 4 for explanation of abbreviations. *LAC* Left anterior chest *RPC* Right posterior chest

With equipment of the Ramsey Watson Weinberg type which has no image intensification a 116-kilovolt setting at 100 milliamperes in the anteroposterior position and 150 milliamperes in the lateral position suffices for the average adult The patient receives a total skin dose in air of 8.9 roentgens with such settings. This dosage is distributed over 360 degrees, as compared to 10 roentgens for an average 2 minute fluoroscopy which is concentrated on slightly over 180 degrees of body surface Filming is at a rate of 15 frames per second

One complete rotation of the patient is recorded on approximately 72 serial exposures (one exposure for each 5 degrees of rotation) These exposures afford views of the heart and lung fields from all angles in the horizontal field and when viewed as a continuous motion picture present a three-dimensional stereoscopic effect This film represents a permanent record of fluoroscopy to which reference can be made at any time

Results and discussion

Publication of cinefluorographic studies as series of still photographs fails to do justice to the method because of the loss of the ciné-effect and of detail in prints which are several generations removed from the original In the preparation of the accompanying illustrations, each image had to be rephotographed and printed four times before the final layout was attained Therefore retouching was utilized in order to preserve detail that was easily visible in the original 35-mm film strips. The layouts include every fourth frame through a complete rotation

The normal subject is presented in Fig 3 The sequence begins with the standard posteroanterior view goes on to the right anterior oblique and right lateral views then to the right posterior oblique and anteroposterior projections. At this point the patient has rotated through 180 degrees. The rest of the sequence runs via the left posterior oblique left lateral and left anterior oblique views back to the starting point. The relationships of the cardiac chambers to the esophagus and lung fields in the standard posteroanterior anterior oblique and lateral views have

been abundantly described[1-4] and are generally familiar to physicians. The posterior oblique contours and relationships are rarely described and seldom used clinically. Fig. 4 depicts the approximate location and identity of the cardiac borders in the right posterior oblique projection. The right anterior lung field is seen on the right, and the left posterior lung field on the left. The right border of the heart consists of the right atrium superiorly and the right ventricle inferiorly. The left border is partly overshadowed by the barium filled esophagus and is made up almost entirely of the left ventricle. Small segments of the left atrium and left pulmonary artery may be discernible high up under the aortic arch.

In the left posterior oblique position (Fig. 5) the right posterior lung field is seen on the right and the left anterior lung field on the left. The right border of

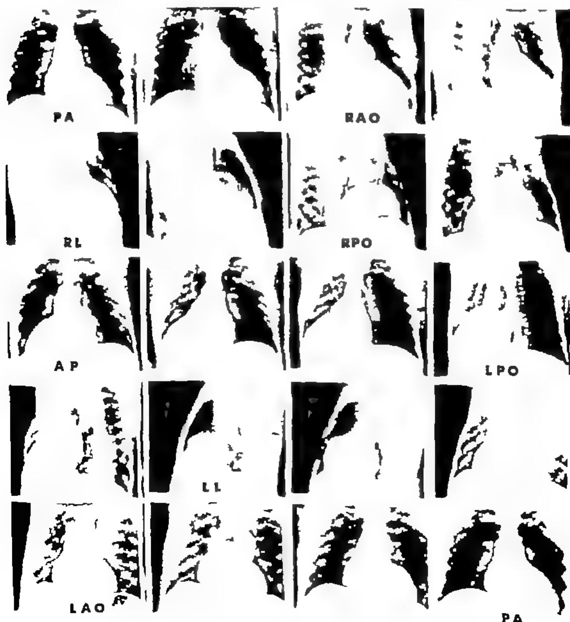


Fig. 6. Left ventricular hypertrophy in patient with hypertensive cardiovascular disease.



Fig 7 Left trial enlargement in pa ien w h mitral regurgit tion. Enlargement of both ventricles is lso present

the heart is now made up from above downward of left atrium right atrium and right ventricle Most of the left border is made up of the left ventricle although the pulmonary outflow tract and left pulmonary artery compose its most superior part just below the aorta.

Left ventricular hypertrophy secondary to hypertensive cardiovascular disease is shown in Fig 6. As the patient rotates, the exterior surface of the left ventricle with the exception of the diaphragmatic portion is well demonstrated in both posterior oblique views, as well as in the left

anterior oblique and left lateral projections. Irregularities and aneurysmal bulging of the left ventricular wall should be easily demonstrable by the method although this is not yet established

Left atrial enlargement in a patient with rheumatic mitral regurgitation is shown in Fig 7 Enlargement of both ventricles and of the pulmonary outflow tract is also present. Not seen in the still views is the pulsation of the pulmonary veins which was easily made out in the movie version

Films taken in a case of a large *bronchogenic carcinoma* located in the anterior and lateral basilar segments of the right lower lobe with metastases to the right hilar nodes, are summarized in Fig 8 The location of the tumor mass in the substance of the lung and its close proximity to the chest wall are discernible especially in the

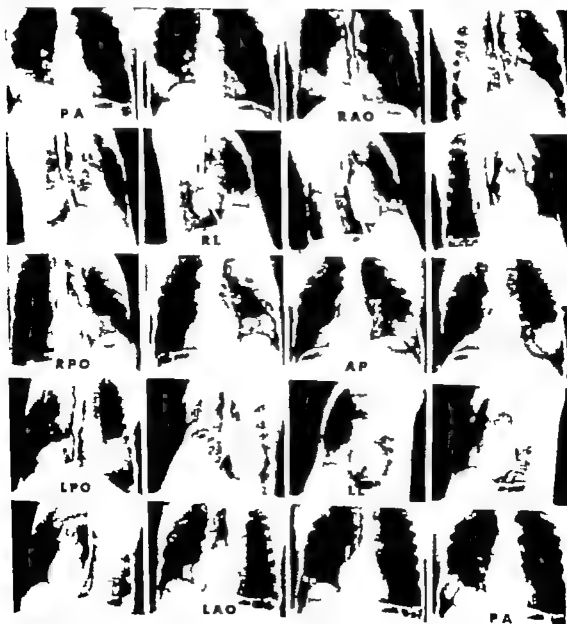


Fig 8 Tumor in right lower lobe. Bronchogenic carcinoma in the right lower lobe with metastases to the right hilar node Paralysis of the right hemidiaphragm was seen in the movie from which the sequence was taken.



Fig. 9 Pulmonary angiogram in a patient with a large bronchogenic carcinoma in the left upper lobe

posteroanterior and left posterior oblique views. Th movies (but not the still print) also provided useful i formation about th relationship of the ma to the bra ches of the pulmonary ascular tree. The same features are seen in iews laid out in Fig. 9. The patient had a large bronchogenic carcinoma located in the posterior part of the left apex. Contr t medium w in jected int the superior vena c a ju t before the film were made. Bran hes of the left pulmon ry artery overlie the tumor in the posteroanterior iew but are shown to be clearly separate from it as the rotation proceed. Vessels which in some iews appear to enter the tumor are traced in tead to superimposed normal lung tissue.

These and other studies suggest several noteworthy advant ges. First, the method provides a permanent fluoroscopic record of cardiac contours and move ent. Second

it permits rather precise localization of lung lesions and when used in conjunction with pulmonary arteriography may provide a fair amount of information on the degree of vascularization of tumor masses. When used in conjunction with bronchography the technique may permit better visualization and localization of bronchial lesions than can be achieved by ordinary methods. Finally the method again raises the possibility that posterior oblique views of the heart and great vessels may have fallen into disuse prematurely. Experience with rotational cinefluorography suggests that they may yield clinically useful information especially in regard to the left ventricular contours.

With the development of better equipment which will permit more precise cinefluorographic recording of pulmonary and cardiac detail the main disadvantages of the rotational method will be overcome. When this is achieved wide application of the method can probably be expected.

Summary

A technique of rotational cinefluorography is described in which the patient is rotated through 360 degrees during filming. An electrically operated rotating chair is employed which automatically alters the x-ray settings to compensate for changing diameters of the chest. The clinical usefulness of the method in localizing pulmonary lesions and in providing permanent fluoroscopic records is already established to a degree. Technical improvements in roentgenographic apparatus are required before the method can be expected to become routine.

The authors gratefully acknowledge the technical assistance of Harold Alsobrook, R.T., Helen Mebane, R.N., and Allen Harrington, of the X-Ray Division, General Electric Corporation.

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Experimental and laboratory reports

The acute effect of alcohol on the circulation and on the oxygen metabolism of the heart

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Alcohol has been considered to be effective in the treatment of angina pectoris since the original description of this syndrome by Heberden.[1-4] The mechanism of the effect is usually ascribed to dilatation of the coronary arteries. Experimental work on this subject however has given conflicting results. Dixon reported a two-phase response to alcohol in the Langendorff preparation as has Cow[6] in ring-strip segments of coronary arteries. Gilbert and Fenn injected a single dose of 240 mg per kilogram into dogs with an open chest and did not observe any change in outflow from the coronary sinus. Lasker and associates carried out similar experiments and reported a rise in coronary blood flow after dosages of alcohol greater than 375 mg per kilogram. Sulzer[9] on the other hand reported a fall in outflow from the coronary sinus after alcohol in the heart-lung preparation. Leighninger and associates observed a decrease in collateral blood flow to the heart when alcohol was administered.

In the present study an attempt has been made to obtain information on the possible mechanism of action of alcohol on anginal pain by studying the general and coronary hemodynamics and oxygen metabolism of the myocardium in intact anesthetized dogs under the influence of alcohol.

Methods

Experiments were carried out on 10 dogs under thiopentone anesthesia. Alcohol 96 per cent, was given intravenously with a constant infusion pump in doses of 51 to 86 (average 58) mg per kilogram per minute for 20 minutes. Measurements were carried out at 10-minute intervals i.e. 10 minutes before the infusion at the moment the infusion was started 10 and 20 minutes after the start of the infusion and 10 and 20 minutes after the end of the infusion.

Cardiac output was measured by thermodilution using a special catheter. This catheter which was closed at the end had a thermistor placed 1 or 2 cm from the tip and a side hole for injecting the indicator 16 to 18 cm from the tip. The tip of the catheter and the thermistor are located in the outflow tract of the right ventricle or in the main trunk of the pulmonary artery the injection opening is then located in the right atrium. The indicator was 5 ml of 5 per cent glucose at a temperature of 19 to 23° C.

Coronary sinus outflow was measured by local thermodilution.[12] An upstream thermodilution catheter (Fig 1) was inserted through the jugular vein into the coronary sinus under fluoroscopic control. In order to measure the entire outflow the catheter segment which contains the in-

With the technical assistance of J Hrabětová and V [illegible].
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jection opening and thermistor should be located about 1 cm. deep into the sinus. This depth can be controlled as follows If the depth is insufficient the thermistor is still in the right atrium so that injection of cold solution anywhere in the venous system will lead to a deflection of the galvanometer within a few seconds. The catheter should be slowly pushed into the sinus until such a control injection produces no deflection of the galvanometer As indicator 1.5 ml. of 5 per cent glucose was injected at a temperature of 19 to 23° C.

In each period cardiac output was measured three times, along with coronary sinus outflow and average values were taken

In addition aortic pressure was measured with an electromanometer pulse rate was measured from the pressure curves, and the oxygen content of arterial and coronary sinus blood was measured with a hemoreflectometer From the data collected we calculated stroke volume total peripheral and coronary resistances in relative units,

$$\frac{\text{mean arterial blood pressure (mm. Hg)}}{\text{cardiac output (L./min.)}}$$

and

$$\frac{\text{mean arterial blood pressure (mm. Hg)}}{\text{coronary sinus outflow (ml./min.)}}$$

respectively the external work of the left ventricle, myocardial consumption of oxygen myocardial extraction of oxygen and the efficiency of the left ventricle

Results

Table I presents changes in the measured parameters in terms of per cent of control values, with standard deviations (S D) statistical significance being indicated for values both during and after infusion Control values represent the average of both measurements previous to the start of infusion.

The infusion of alcohol resulted in a significant decrease in cardiac output because of the decrease in stroke volume. Arterial blood pressure did not change i.e. there was a rise in peripheral resistance. Coronary sinus outflow increased slightly as a result of a fall in coronary resistance perfusion pressure remained unchanged. External work of the left ventricle decreased because of the decrease in cardiac output Myocardial oxygen consumption increased in parallel with the rise in coronary flow Oxygen content in the coronary sinus did not change, nor did the amount of oxygen extracted by the myocardium The arteriovenous difference in oxygen content across the myocardium remained without change. The rise in myocardial oxygen consumption in the presence of a decrease in external work of the left ventricle means that the efficiency of the left ventricle decreased

Discussion

As stated in the introduction the positive effect of alcohol in angina pectoris has been explained in terms of vasodilation of the coronary vessels and increased coronary blood flow In our experiments, coronary vascular resistance did decrease, resulting in a rise in coronary blood flow However this effect was accompanied by a rise in oxygen consumption despite the decrease in cardiac output and the lack of change in pulse rate and mean arterial blood pressure. It would appear therefore that alcohol has a direct effect on the myocardium and that the rise in coronary



Fig 1 Diagram of the coronary sinus thermodilution catheter *T* Thermistor *I* Injection opening which has diameter of 0 6 or 0 7 mm The catheter has two lumens In one of these are the thermistor leads, coiled for greater elasticity and the other lumen serves for injection. The distance between the injection opening and the thermistor is 3 mm The thermistor is located 15 mm. from the tip of the catheter The diameter of the catheter is 2 6 mm and the length is 40 to 45 cm

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Tabl 1

	C l al	Du ng nfusion of lcohol		After i fusion of alcohol	
		10 minut hanges (%)	20-m ule changes (o)	10-m ut ha ges ( )	20-min t changes (%)
C rdiac output Standard deviation Statist l signific nc	3,546 ml./m ±4 8	−14 9 ±19 1 p < 0 05	−23 0 ±20 3 p < 0 01	−20 4 ±19 8 p < 0 02	−17 8 ±19 5 p < 0 05
Mea rterial blood pressure	129 mm Hg ±4 9	−0 4 ±13 8 p > 0 90	+2 3 ±17 0 p > 0 60	+5 0 ±18 1 p > 0 40	+5 9 ±17 7 p > 0 30
Total peripheral resistance	37 1 relati units ±6 1 %	+20 2 ±26 6 p < 0 05	+42 7 ±34 0 p < 0 01	+37 2 ±27 0 p < 0 01	+34 4 ±30 2 p < 0 01
Coronary sl ns flow	120 1 ml./mi ±6 7 %	+12 8 ±13 0 p < 0 02	+12 8 ±17 0 p < 0 05	+12 0 ±17 9 p > 0 05	+10 4 ±21 4 p > 0 10
ronary resist nc	1 24 relati e nit ±8 9%	−12 4 ±11 8 p < 0 02	−8 4 ±17 5 p > 0 10	−5 2 ±18 1 p > 0 30	−3 2 ±18 4 p > 0 50
Heart t	153/mi ±4 0	+2 7 ±13 2 p > 0 50	+4 7 ±16 5 p > 0 30	+5 6 ±17 0 p > 0 50	+5 1 ±16 7 p > 0 30
troke lume	24 0 ml ±5 4	−16 9 ±19 4 p < 0 05	−27 4 ±21 0 p < 0 01	−22 8 ±20 6 p < 0 01	−22 2 ±17 0 p < 0 01
L ent lar external work	6 3 kg./ml ±7 8	−14 1 ±24 5 p > 0 10	−21 0 ±28 3 p < 0 05	−14 5 ±30 0 p > 0 10	−11 4 ±28 8 p > 0 20
terial x gen ontent	17 8 ol ±0 7	+8 1 ±10 1 p < 0 05	+5 0 ±12 7 p > 0 20	+6 6 ±7 2 p < 0 02	+7 2 ±7 4 p < 0 02
ronary sinu ox gen content	6 5 ol % ±3 8	+12 2 ±17 6 p > 0 05	+3 7 ±20 0 p > 0 50	+10 1 ±15 9 p > 0 05	+8 1 ±14 9 p > 0 10
ronary arteriovenous difference of oxygen ontent	11 3 % ±3 3	+5 9 ±16 2 p > 0 20	+3 0 ±21 2 p > 0 60	+5 3 ±18 4 p > 0 30	+8 4 ±14 9 p > 0 10
ocardi l oxygen extraction	61 7 ±3 3	−3 0 ±9 5 p > 0 30	−2 4 ±11 6 p > 0 50	−2 3 ±11 9 p > 0 60	+1 1 ±8 1 p > 0 50
entric la oxygen consumption	13 8 ml./m ±7 5%	+10 3 ±16 1 p < 0 01	+15 4 ±28 3 p > 0 10	+16 7 ±22 4 p < 0 05	+18 1 ±22 3 p < 0 05
entricula ffi iency	11 7 ±11 1	−27 9 ±19 7 p < 0 01	−28 6 ±28 3 p < 0 02	−25 4 ±28 1 p < 0 05	−25 0 ±22 3 p < 0 01

flow was a result of the increase in myocardial oxygen consumption rather than a direct effect of alcohol on the smooth muscle of the coronary vessels. In this case one can hardly state that such a rise in coronary blood flow is of clinical advantage in angina pectoris. However it is clinical experience that the pain of angina pectoris is decreased by alcohol. Why? Evans and Hoyle[13] have shown that alcohol depressed the pain of angina pectoris to the same degree as did nitroglycerin but in only 1 of 11 patients was this associated with an increased ability to do work. According to Stearns and associates,[14] a therapeutic dose of whiskey does not shorten the duration of anginal attacks nor does it increase the work capability during an attack. Russek and associates[15] observed only a decrease in pain after giving alcohol during anginal attacks but no improvement in the electrocardiographic changes in an exercise test, in contrast to the effects of nitroglycerin and papaverine.

These controlled clinical studies, therefore, could show no favorable effect of alcohol on the pathophysiologic basis of anginal pain, i.e. acute coronary insufficiency. This is in agreement with our experimental findings which bring no evidence to bear that there is a specific effect of alcohol which might improve the defect present in angina pectoris. Thus the principal effect of this drug would appear to be in changing the patient's threshold to pain.

Summary

Alcohol in an average dose of 58 mg per kilogram per minute was infused during 20 minutes into 10 anesthetized dogs. Cardiac output and the external work of the heart decreased with no change in arterial blood pressure. Coronary sinus outflow increased as a result of a fall in coronary vascular resistance. There was no change in either coronary arteriovenous oxygen difference or myocardial oxygen extraction. Oxygen consumption however increased in the myocardium. The results are discussed in terms of the effect of alcohol on the pain of angina pectoris.

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The connecting pathways between the sinus node and A V node and between the right and the left atrium in the human heart

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Ever since the discovery of the sinus node[1] and A-V (atrioventricular) node,[2] a sustained controversy has existed concerning the question of specialized pathways between these two structures. Of the various studies which claim to demonstrate an internodal tract, as reviewed by Pace, the most noteworthy have been those of Thorel[3] and Wenckebach.[4] A third tract was partially described by Bachmann, who was concerned only with its interatrial and not internodal conduction. Subsequent denial of the existence of any one of these internodal tracts as summarized by Lev has profoundly influenced present concepts of internodal conduction. The conflicting viewpoints have been reviewed recently by Robb and Petri and by Truex.

Much of the confusion about this question may be attributed to the assumption that such tracts must be "specialized" tissue and to what the morphologic features of such tissue should be, particularly in man. Two points serve to indicate how unnecessary this confusion is. First, the sinus impulse must arrive at the A-V node by some regular route or routes since orderly performance of the normal heart demands it and millions of electrocardiograms attest to it. Second, recent studies have demonstrated unequivocally that the speed of conduction between the nodes (at least in experimental animals) is of such an order that conduction must occur over physiologically specialized pathways.

Therefore, the question is not actually whether connecting pathways exist, but where they are. Whether the tissue in these pathways may be clearly identified as "specialized" by current methods for morphologic study depends a great deal on how reliable such methods are.

Material

As part of a continuing study of the normal and abnormal human cardiac conduction system, the region between the sinus node and A-V node has been examined by subserial sectioning in 69 human hearts. Techniques used for examining the sinus node and A-V node have been reported previously. Pertinent to the present report, sections were made at intervals of 2 mm. in a radial distribution about the superior vena cava, with those sections through its anterior and medial aspects transecting Bachmann's bundle (the an-

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terior interatrial myocardial band) and the anterior portion of the interatrial septum extending down to the interventricular septum. From the posterior margin of the superior vena cava to the anterior margin of the inferior vena cava (thus through the entire sinus intercavarum) 2 mm. sections perpendicular to the interatrial septum included the crista terminalis, sinus intercavarum and the septum down to the A V node All the sections together thus included the interatrial septum in continuity From the anterior margin of the inferior vena cava posteriorly sections were made perpendicular to the internal surface of the Eustachian ridge as it curved toward the coronary sinus and posterior margin of the A V node

For the purpose of demonstrating fiber to-fiber continuity serial sections were made in 4 additional hearts at 6-micron intervals, with every tenth section mounted The plane of these sections through the sinus intercavarum and interatrial septum was selected to include both the sinus node and A V node. In 3 other hearts, horizontal sections were made at 2-mm intervals from the mid-level of the interatrial septum down through the upper interventricular septum. These were particularly useful to show the approaches to the A V node from its anterior and posterior margins.

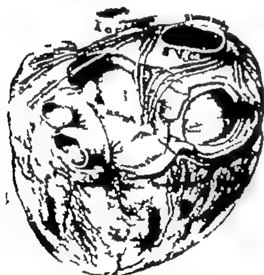


Fig. 1 A drawing of the heart to demonstrate the internodal and interatrial conduction pathway in man Bachmann bundle is slightly exaggerated in size for the sake of clarity the division of fibers into ones going to the left atrium and others to the A V node is shown The cutaway portion of the drawing interrupts fibers in the middle internodal tract which inconstantly cross to the left atrium. Relationship of the anterior and middle internodal tracts to the septum ovale (S O) and membranous portion of the interventricular septum (M S) is indicated The U-turn of the coronary artery which supplies the A V node is a characteristic anatomic feature The fibers which ascend along the left atrial side of the interatrial septum from the region of the A V node are not shown.

To supplement the histologic studies described above the regions between the sinus node and A V node were examined by gross dissection in 42 additional hearts, in a manner similar to that described by Papez.[8] Particular regions pertinent to this report, in addition to the immediate environs of the two nodes, included the crista terminalis (residual of the septum spurium) Bachmann's bundle, the sinus intercavarum Eustachian ridge (valve of the inferior vena cava) and the entire interatrial septum

Results

In all the hearts continuous bundles of myocardium could be demonstrated histologically in three regions between the sinus node and A V node (Figs. 1 3) These were well enough developed and of sufficient size to be followed without difficulty in the additional hearts dissected grossly The myocardial bundles correspond to the tracts described by Bachmann Wenckebach and Thorel In some hearts one tract was better developed than the others

In all three tracts, fibers with Purkinje characteristics (Fig 4) were abundant but none of the tracts was composed exclusively of these fibers, nor were the Purkinje fibers continuous being interrupted by ordinary fibers in many sections. Occasionally a lengthy segment of Purkinje fibers was encountered but these segments occurred in different portions of the three tracts from heart to heart.

The respective lengths of the three internodal tracts potentially an important factor in determining preferential conduction of the sinus impulse to the A V node are of questionable reliability when measured in the postmortem heart. In general



Fig. 2. Dissection of a normal human heart viewed from directly above the atria. X marks the location of the sinus node, and the broken lines indicate the routes of the internodal and interatrial pathways. (The same series of broken lines are used in Figs. 3 and 5.) The dots follow the anterior internodal tract and the major interatrial tract, which begin together. The double-line dashes follow the middle internodal tract. The single bold-line dashes follow the posterior internodal tract.

the lengths of the anterior and middle internodal tracts were nearly equal and both were shorter than the posterior internodal tract. However, in various hearts these measurements varied so greatly as to make their significance in the present material doubtful.

Anterior internodal tract. The anterior internodal tract leaves the sinus node in a forward direction and curves about the superior vena cava and anterior wall of the right atrium into Bachmann's bundle, where it divides into two bundles of fibers (Figs. 1-6). It should be noted that Bachmann described only one of these divisions since he was concerned only with interatrial conduction and made no mention of internodal conduction from this direction. The division which Bachmann studied continues into the left atrium, whereas the other division curves back into the anterior portion of the interatrial septum. In the septum this latter division of fibers descends obliquely behind the root of the aorta (the noncoronary sinus) to enter the anterior part of the superior margin of the A-V node. A ul h n on just above the node is discussed below. Continuity of this internodal tract could be established in all the hearts studied histologically, and the myocardial fibers were in bundles of a size which made them simple to dissect grossly. Throughout most of its course in the interatrial septum, but particularly near the A-V node, this tract merges with myocardial fibers from the second or middle internodal tract.

Middle internodal tract. The middle internodal tract, corresponding to Wenckebach's bundle, leaves the dorsal and posterior margins of the sinus node and curves be-



Fig. 3. The interior of the human right atrium and right side of the interatrial septum are shown with the internodal pathways indicated by the same lines as in Fig. 2. The broken X lies beneath the sinus node, which is epicardial in location. The arrow on the right is in the ostium of the superior vena cava, and the one on the left indicates the ostium of the inferior vena cava, which has been cut through to open the atrium along the atrioventricular sulcus. The free wall of the atrium is lifted directly upward. All three internodal tracts converge at the A-V node, which corresponds to the parentheses. The Eustachian ridge, through which the posterior internodal tract passes, is well developed in this heart. The Thebesian valve of the coronary sinus may be seen just beneath the septal insertion of the Eustachian ridge.

hind the superior vena cava to course through the sinus intercavarum into the dorsal portion of the interatrial septum (Figs. 1 3 and 7) Fibers in this tract descend from the sinus intercavarum along the right atrial side of the upper interatrial septum into the superior margin of the A V node It is in this latter region that the merging with fibers which curve back from Bachmann's bundle is particularly observed (Fig 6) Of the three internodal tracts continuity of muscle bundles was most variable in Wenckebach's region with scattering of myocardial fibers in fat near the top of the interatrial septum (Fig 7) On serial sectioning continuity of these fibers to the A V node was established However fibers from this tract seldom cross directly over to the left atrium in the manner reported by Wenckebach.

Posterior internodal tract. The posterior internodal tract leaves the posterior margin of the sinus node to enter the crista terminalis, following it through its entire course to the region of the Eustachian ridge (Figs. 1 3 5 6) Lateral extensions from these fibers arborize over the dorsum of the right atrium and probably deliver the sinus signal to it The fan-like distribution of myocardial traberulae from the crista terminalis to the body of the right atrium forms an interesting geometric design consonant with the function of these trabeculae in distributing the sinus impulse Fibers which continue from the crista terminalis into the Eustachian ridge follow this structure to the A V node. As they enter the septum these fibers cross over the coronary sinus and arrive at a point just above the posterior margin of the A V node, turning down rather sharply to enter the node or bypass it.[11] The size of the Eustachian ridge varies considerably in different hearts and in some it is a thin fold resembling a false tendon in such cases it is composed largely of Purkinje fibers. In essence this is the tract described by Thorel and more recently suggested by Söderström[1] to be an important route of internodal conduction Fibers in this tract do not continue directly to the left atrium except via their connections with the other two tracts at the level of the A V node (see below) Like the anterior internodal tract this one is usually so well developed that it is demonstrable by simple gross dissection especially in hearts with a prominent Eustachian ridge

Interatrial conduction Although the primary purpose of this study was to search for internodal pathways, the material was equally suitable for investigation of interatrial connections. As mentioned under consideration of the separate internodal



Fig 4 A myocardial fiber from human heart, demonstrating the Purkinje characteristics of coarse myofibrils and the perinuclear clear zone and bulge Goldner trichrome stain, X480.

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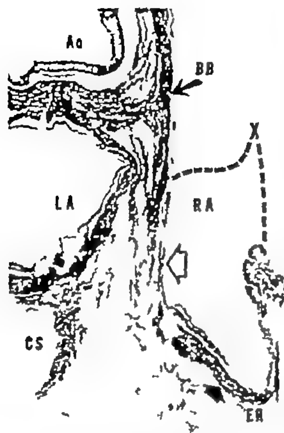


Fig. 5. A photograph (slightly enlarged) of a horizontal section through the human interatrial septum demonstrating the internodal and interatrial conduction paths. X indicates the location of the sinus node, which is above the plane of this section. The open arrow indicates the location of the A-V node, which is below the plane of this section. The short broad black arrow points to fibers in the posterior internodal tract as they approach the A-V node from the Eustachian ridge (*ER*); there is a pathologic focus of fibrosis near the A-V nodal end of this tract. Bachmann's bundle is indicated by the narrow black arrow and the letters *BB*. Note its division into fibers which continue into the left atrial wall and others which descend obliquely in the interatrial septum toward the A-V node. The latter fibers are joined by fibers from the middle internodal tracts. The dots and dashes correspond to the ones in Figs. 2 and 3. *A*, Aorta. *CS*, Coronary sinus. *RA*, Right atrium. *LA*, Left atrium.

tracts, there were no direct continuations of myocardium from the Eustachian ridge to the left atrium, and only sparse connections across the dorsum of the interatrial septum (Fig. 7). However, in every heart there was an easily demonstrable continuous bundle of myocardium crossing the anterior margin of the interatrial septum as originally described by Bachmann, who proposed it as the preferential route of interatrial conduction on the basis of both anatomic and physiologic studies in the dog. That it most likely serves the same function in man is suggested by its direct continuation in the human heart with the sinus node at its right end and its distribution into both the atrial appendage and the body of the left atrium at its left end (Figs. 1 and 2). It is of further interest that the human sinus node artery always provides a major branch to Bachmann's bundle. When this artery arises from the left coronary artery (in about 45 per cent of human beings[17]) it virtually always courses directly through Bachmann's bundle to reach the sinus node. When it arises from the right coronary artery (55 per cent) it virtually always divides so as to supply both the sinus node and Bachmann's bundle.

In addition to interatrial connections through Bachmann's bundle, which are the most direct anatomically and may be expected to function as the preferential route physiologically, there are other potential interatrial connections, but they are much longer for the sinus impulse to travel. These connections are found just above the level of the A-V node in the interatrial septum where all three internodal tracts communicate with each other. The junction of internodal tracts at this point also joins with myocardial fibers which are located along the left atrial side of the septum and must be considered capable of distributing an impulse from the juxtanodal communications to the left atrium. Because this would represent such a long pathway for the sinus impulse to reach the left atrium, it is probable that it does not function unless the preferential route through Bachmann's bundle is disrupted or the pacemaker site is not in the sinus node.

Divisions and functions of the internodal tracts. As fibers from the anterior and middle tracts approach the A-V node, they divide into two groups in the same manner as do those from the posterior tracts, and in each case some fibers enter the node whereas others join the bypass tracts[11] (Fig. 8). Thus fibers which enter the bypass tracts not only have the opportunity of shortcircuiting the A-V node but also

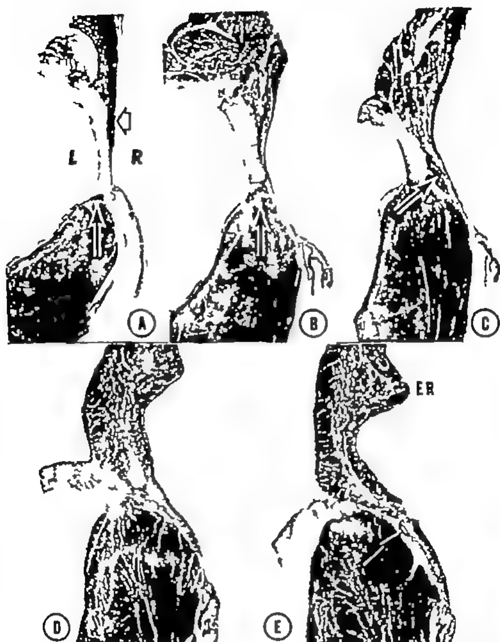


Fig. 6. A series of photomicrographs from human heart, prepared as ertical sections hrough the interatrial septum, pproximately 2 mm part. From *A* t *E* the sections proceed from anterior posterior thus, *A* is through the membranous septum, anterior to the A-V node, and *D* and *E* are through the Eustachia ridge (*ER*) posterior to the A-V node. I *A* the arrow points to the anterior end of the A-V bundle nd its left bundle branch; *L* and *R* are the lef and righ sides of the membranous septum, w th he same orientation pplicable to the other sections the open arrow indicates the obliquely descending fibers from he nterior internodal tract as they course posteriorly toward the A-V node. I *B* the rrow indicates the posterior margin of the A-V bundle with the origin of the left bundle branch. Fibers from both the anterior and middle internodal tracts merge above the A-V node in both *B* nd *C* with the arrow in *C* indicating the A-V node t h nterior end fibers entering the bypass tracts can be seen. *D* is through the posterior margin of the A-V node with the fibers of the posterior internodal tract well shown as they descend forward from the Eustachian ridge (*ER* ▤ *E*). I both *D* and *E*, some fibers of the posterior internodal tract descend t the base of the tricuspid valv as they course anteriorly toward the A-V node and its bypass tracts The arrow in *E* indicates the A-V node artery which ca also be identified in *D*. See Fig. 8 for more detailed iew of the relationship of the internodal tracts to the A-V node

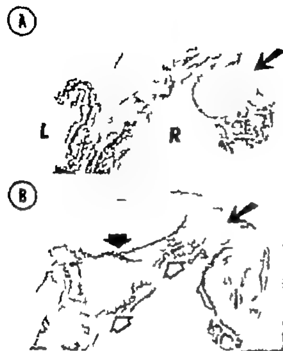


Fig. 7. Two photomicrographs of the sinus node and upper interatrial septum made 4 mm. apart with the ... B. The sinus node is indicated by the narrow arrow in each. The L and R in A indicate the left and right sides of the septum. In B the fibers of the middle internodal tract (the open arrow) can be seen extending from the sinus node along the right atrial side of the septum toward the A-V node, but fibers crossing directly over the septum to the left atrium as indicated by the broad black arrow are sparse. In various hearts they are only inconstantly present. These interatrial fibers, described by Wenckebach, are not considered to be as important to interatrial conduction as are those passing through Bachmann's bundle.

provide a potential route of continuity between all three internodal tracts. The possible significance of this in relation to circus movement and atrial arrhythmias is discussed later.

In addition to communication between all three tracts within the A-V nodal bypass fibers from all three tracts communicate with each other in crossovers or decussation directly above the node; this junction has been discussed in a previous study on the morphology of the A-V node.[11] The junctions above the node which may be termed supranodal offer no opportunity for circumventing the A-V node to reach the ventricles and thus differ in an important manner from the junction in the bypass tracts, which can circumvent the bulk of the node. Free communication between fibers in the bypass tracts therefore has two potential functions: circumventing the A-V node during atrioventricular conduction and additionally allowing communication between the three internodal tracts. There are thus two areas of junction between the three internodal tracts near the A-V node: *supranodal* junction above the node and *paranodal* junction within the bypass tracts. It is important not to confuse these paranodal fibers with the paraspecific fibers of Mahaim[8] which are said to course from the A-V bundle (not the node) directly to the interventricular septum and which in view of modern electrophysiologic concepts (the delay in A-V conduction being at the atrionodal junction) are of doubtful physiologic significance.

Discussion

It is unclear why there has been controversy concerning the existence of fiber tracts from the sinus node to the A-V node in the human heart unless it is because of persistence in attempts to demonstrate tracts composed exclusively of fibers with specialized morphologic characteristics. It is clear that continuous bundles of myocardial fibers exist in all three of the regions described by Bachmann, Wenckebach, and Thorel.

Morphologic features of rapidly conducting fibers in the human heart have as yet not been satisfactorily defined. That fibers with characteristic Purkinje features—coarse myofibrils, perinuclear clear zone ("sarcoplasm"), greater transverse diameter, large rectangular nuclei—exist particularly in regions in which rapid conduction is believed to occur suggests certainly that fibers with these characteristics conduct more rapidly than do most ordinary myocardial fibers. However, to assume that myocardial fibers with ordinary appearance by present histologic techniques necessarily conduct slowly is proved to be erroneous by the demonstration of such fibers in the human A-V bundle as well as portions of the bundle branches. True has recently summarized current knowledge of Purkinje fibers in various species and has emphasized the difficulty in identifying these in man, especially in their inter-

mediate or transitional forms. Much of the confusion in regard to these fibers in man, he indicates, arises from the mistaken concept that they should resemble the more commonly described *Purkinje* fibers of ungulates, which they do not.

Since the exact morphologic characteristics of all rapidly conducting fibers in the human heart are unknown, it seems reasonable to believe that the sinus impulse in man is delivered to the A-V node through one or more of the three pathways described, which contain abundant fibers usually thought to conduct rapidly but which are not entirely composed of these. Unless it is believed that the sinus impulse passes over one or more of these three tracts to the A-V node which are the sole myocardial connections between the nodes, one is left with no explanation of its route at all. The commonly used explanation of "syncytial" spread through atrial myocardium has never been structurally defined. Except for the three tracts described above, the only large volume of tissue present in this region is fat, which has one of the highest resistances of all biologic tissue to electrical conduction, presumably because of its low electrolyte content.[3]

Embryologically, there is good reason to anticipate that specialized myocardium, whether morphologically identifiable *in man* as such, should exist precisely in the region encompassed by the two nodes and the three internodal tracts. This region, including the ostia of both venae cavae and the coronary sinus, is derived from the primitive sinus venosus, which in lower forms (e.g., the frog and turtle) remains an entirely specialized area in the electrophysiologic sense. In the frog, for example, Weidmann[26] has recorded action potential from the entire sinus venosus which is completely different from action potential from the free wall of atrium. Although prepotential has a faster build-up in the region of the pacemaker, there is rising prepotential in all the tissue of the sinus venosus. Whether this same characteristic is true of the three internodal tracts in man is unknown, although their existence as the only remaining myocardium in this region derived from the sinus venosus leads one to suspect that it may be.

In addition to comprising the general boundaries of the region of the primitive sinus venosus, the three internodal tracts also outline the area commonly employed to explain circus movement as a mechanism in atrial arrhythmias. These circus movements encompass the mouths of the venae cavae just as do the anterior and posterior internodal tracts (with the middle tract passing between). Although there is disagreement about the validity of the circus movement theory, it has not previously been clear what anatomic structures were involved. A brief examination of the topography outlined by the three *internodal* tracts indicates at least three internodal



Fig. 8. Photomicrograph of section through the middle of the A-V node (indicated between the two small black arrows), enlarged about 15 times. Decussation of fibers above the A-V node are well shown. M and T indicate the bases of the mitral and tricuspid valves. The curved arrow on the left indicates fibers from the anterior and middle internodal tracts, dividing to enter the A-V node as well as the bypass tract (open arrow). The curved arrow on the right indicates fibers from the posterior internodal tracts which similarly divide ... both

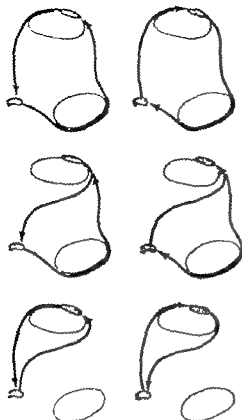


Fig. 9. Possible directions of circus movements involving the internodal tracts. The arrows indicate the direction of movement. For orientation concerning the sinus node, superior vena cava, A-V node, and inferior vena cava, see Fig. 1, from which this diagrammatic sketch is derived.

and reverse directions, doubling this to six (Fig. 9). An impulse which originates in the direction of one limb of such a circle could return by either of the other two tracts.

This leads to the consideration of how the impulse from the sinus node normally travels to the A-V node. Classic experimental studies by Eyster and Meek[22] have indicated that A-V dissociation can be produced temporarily by cuts in the region of any one of the three tracts, and permanently by cutting all three. The cuts by Eyster and Meek were not intentionally related to specific internodal tracts, but were placed to encompass the possible routes of exit of an impulse from the sinus node. It is remarkable, therefore, how accurately they interrupt the exact pathways being described here. Furthermore, their cuts on the four sides of the sinus node were not equally effective in interrupting conduction from the sinus node to the A-V node, evidence which must be considered to favor conduction along specific pathways rather than in a syncytial manner. The cut which they found to be most effective in interrupting internodal conduction was along the caval border of the sinus node, which would in effect disrupt all the middle internodal fibers, most of the anterior internodal fibers, and a variable number of the posterior internodal fibers. Conversely, the only one of the four cuts which they found to be completely ineffective was along the right atrial border of the node, where none of the internodal tracts would be disrupted.

In man, a number of questions about the physiology of internodal conduction are immediately apparent. Does the sinus impulse employ only one tract, and if so, which one? Is it the same tract in all human beings, or is it the same tract in the same person all the time? If it is a single tract and varies from person to person or in the same person from time to time, what are the factors which govern selection of the tract? Perhaps the sinus impulse travels along all three tracts all the time normally, and a means of synchronization of arrival at the A-V node exists, or a means of cancellation of late-arriving impulses is available. Simple nonresponsiveness of an A-V node already stimulated by an earlier signal may be such a protective mechanism. This arrangement would provide the safety measure of at least one impulse being able to reach the A-V node from the sinus node in the event that one or two of the three tracts were injured or diseased.

As the three tracts descend through the interatrial septum toward the A-V node, each divides to send fibers both into the node directly and along special bypass tracts beside the bulk of the node, which re-enter the lower margin of the node. These bypass tracts have been postulated as the alternate route for dual A-V conduction,[23] the existence of which was first suggested by Moe and his colleagues[24] on the basis of physiologic studies. The additional function of these bypass tracts as a paranodal communication between all three internodal tracts has been described above.

along with a second area of supranodal junction Circus movements may be either cancelled or made continuous at either the supranodal or paranodal points of juncture between the three internodal tracts.

In keeping with current interest in quantitative morphology [34] it may be noted that the internodal pathways and the route of an impulse traveling over them resembles a Möbius ring which has its twist at the A V node (Fig 10) The upper limb of the ring is composed of a curve about the two cavae whereas the remaining portion of the ring is in the interatrial septum bending sharply at the level of the A V node. A split in the curve around the superior vena cava would permit inclusion of both the anterior and middle internodal tracts although this arrangement is omitted in the drawing for simplicity Since an elementary problem in the science of topology concerns the possible continuous travel of a point on both surfaces of a plane without leaving the surface or crossing an edge, which can occur only on a Möbius ring or similar structures, the possible relationship to circus movement in cardiac electrophysiology is quite apparent



Fig 10 A Möbius ring is superimposed on the anterior and posterior internodal tracts, with its twist at the level of the A V node where fibers from all three internodal tracts decussate See text for discussion.

From anatomic considerations alone it seems likely that the preferential route of interatrial conduction must be through Bachmann's bundle which is not only consistently present but is also the most direct route from the sinus node to the left atrium. It should be noted however that one longer route for interatrial conduction (from the sinus node to the region of the A V node and thence up the left atrial side of the interatrial septum) is longer only relative to cardiac rhythms originating in the sinus node During A V nodal rhythm for example conduction to the left atrium would most likely occur up the left atrial side of the septum just as conduction to the right atrium would spread up one or more of the internodal tracts to distribute to the free wall of the right atrium

Summary

In the human heart there are three connecting pathways between the sinus node and the A V node, all of which contain Purkinje fibers but also many myocardial fibers without these characteristics. The anterior internodal tract passes from the sinus node to sweep anterior to the superior vena cava into Bachmann's bundle where it divides to distribute to the left atrium and to curve back into the interatrial septum and descend to the A V node. The middle internodal tract leaves the dorsal and posterior margins of the sinus node and courses behind the superior vena cava through the sinus intercavarum to the crest of the interatrial septum and there descends into the A V node merging with fibers from the anterior tract as it approaches the node. The posterior internodal tract follows the crista terminalis from the sinus node to the Eustachian ridge and thence through the ridge to the posterior margin of the A V node.

Together these three tracts, the two nodes the ostia of both venae cavae, and the coronary sinus, comprise the general outline of the primitive sinus venosus. Reasons why the myocardium in this region may be anticipated to have specialized function are discussed Although demonstration of internodal pathways does not establish the validity of the theory of circus movement, possible circles composed

of lin bs of the three internodal tracts lend anatomic support to such a theory

On the basis of n. tomic considerations, o iduc tion fro n the sinus node to the left atrium is believed to occur preferentially through Bachmann s bundle An alternate interatrial pathway which is much longer for the sinus impulse spreads from the septal portion of the internodal tracts to the left atrium

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An investigation to devise a technique for the production of maximal flows of blood in the arm

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The purpose of this study was to devise a technique which would cause a maximal flow of blood into the arm without recourse to prolonged ischemia, a technique whereby a large part of the resistance to the flow of blood would be offered by the arterial trunk.

The principle which underlies this method is a modification of the circulation in the limb so that arteriolar resistance is lowered and then the measurement of the initial flow of blood into the limb after the release of a suprasystolic cuff pressure.

The flow of blood measured under these circumstances has been termed *arterial blood flow*. It is suggested that these are the maximal flows of blood that the arterial trunk will allow at the existing central arterial pressures. The term *arterial flow* has been adopted since it best indicates the phenomenon in which the resistance to flow lies largely in the arterial trunk. This term distinguishes it from *blood flow* which is usually applied to the measurement obtained by venous occlusion plethysmography, where the resistance vessels (arterioles) are largely involved in hindering the flow of blood. This concept of arterial flow has already been suggested by Landowne and Landowne and Katz, who used prolonged period of ischemia.

Procedure

The subject sat quietly in a heated room (32 to 35°C.) and the forearm and hand were immersed in a water bath at 44°C for 10 minutes. This allowed adequate time for a steady state to be established. The stages of the technique were as follows:

1. The limb was elevated at 10 degrees from the vertical for 30 seconds to permit maximum drainage (Mackay[4]).

2. In elderly subjects, elevation of the arm may not cause the veins to collapse completely, perhaps because of sclerotic changes. Therefore centripetal manual massage from the hand to the pressure cuff was applied four times with warm soapy hands to assist the drainage; at the fourth massage a suprasystolic cuff pressure was applied to a sphygmomanometer cuff on the upper arm.

3. The arm, lubricated with soap, was then thrust into the plethysmograph, which was held in a vertically dependent position. This dependent position is an important and essential part of the technique.

4. After 15 seconds the pressure in the cuff was suddenly released, allowing a rapid inflow of blood into the forearm and hand.

A somewhat similar approach has been

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Table I

	Arterial flows with limb dependent		*VOP with limb horizontal*	
	(c.c./100 c.c./min.)	*% of Control*	*(c.c./100 c.c./min.)*	*% of Control*
Control	42	100	5.2	100
Ischemia (2 minutes)	41	98	25	480
Exercise (40 hand contractions in 30 seconds in occluded limb)	45	107	28	510

the smaller nozzle was reduced. This pressure will depend upon the size of the nozzle relative to the hose. When the nozzle is only slightly smaller than the hose a small pressure applied to the hose may cause the flow through the nozzle to be reduced. However, when the nozzle is smaller than the hose a larger amount of compression will have to be applied to the hose before flow through the nozzle is reduced. This explains why in the case of the VOP technique (when the nozzle of the resistance vessels is in position) an additional 20 mm. Hg of cuff pressure is required to cause a reduction in blood flow as compared with the pressure that causes a reduction in flow when the arterial flow technique is employed (i.e., when the resistance nozzle has been removed).

An important point in support of this thesis that an arterial phenomenon is being examined is that the first reduction in flow occurs when the residual cuff pressure is near to the diastolic value, since the brachial artery is unable to be closed for a small fraction of the pulse cycle without impairing the level of arterial flow.

5. RESIDUAL VOLUME. In this procedure the drainage of the vessels of the limb creates a situation in which the blood vessels may be only partly drained. It is suggested that one of the factors which influences the arterial flow may be the residual volume in the limb after drainage. This residual volume can be diminished by centripetal massage of the limb. The massage applied was that of ten very vigorous centripetal strokes during the last few seconds of drainage of the limb. The results are shown in Table II. An increase of 47 per cent in the refilling volume was accompanied by an increase in arterial flow of only 7.9 per cent.

After shorter periods of drainage in the first stage the initial arterial flow rate was unaffected until the volume of drainage was markedly reduced.

Another procedure which influences the residual volume is digital compression of the subclavian artery. Digital compression of the subclavian artery against the first rib was carried out during the last 10 seconds of the first stage of the procedure whereby the vessels are drained with the limb in the elevated position. The average amount of blood necessary to refill the limb increased by 18.8 per cent, whereas the arterial flow increased by only 8.4 per cent. The additional drainage produced by these procedures does not affect the level of arterial flow appreciably but does serve to empty the veins more efficiently so that when the flow is recorded with the limb dependent the hydrostatic effect of dependency is maintained for a longer period of flow.

6. PRODUCTION OF AN ARTERIAL THROUGH FLOW IN THE FOREARM. The rate of arterial flow in the hand per unit of tissue is larger than that entering the forearm. This greater capacity for arterial flow into the hand permitted the design of a maneuver whereby a transit or through flow in the forearm could be estimated by the procedure described here for measuring rates of arterial flow. The flow is so rapid that the lateral pressure may be reduced and consequently does not have a perfusion pressure high enough to cause a maximum flow through the dilated vessel which branch from the arterial trunk into the tissues of the forearm.

Such rapid high velocity through flows support the thesis that the larger pre resistance vessels are involved in the measurements of arterial flow

The following procedures demonstrate this phenomenon A forearm plethysmograph is placed in position with the usual proximal collecting cuff and with a pressure cuff around the wrist distal to the plethysmograph Two procedures were adopted First, the procedure described for measurement of arterial flow was used but immediately before the release of the occluding cuff proximal to the plethysmograph the cuff distal to the plethysmograph was inflated to 40 mm Hg thus creating a collecting cuff for the hand which stopped venous return from the hand from entering into the segment of the limb in the plethysmograph The flow into the forearm segment was measured. Secondly the first procedure was repeated but immediately prior to the release of the occluding cuff proximal to the plethysmograph the wrist cuff was inflated to occlude completely the circulation both to and from the hand

In the first procedure, the blood surges *through* the segment of the limb in the plethysmograph at a rapid rate and gives an average flow value (7 experiments) into the tissues of the forearm segment of approximately 25 4 c.c 100 c.c./minute In the second procedure in which the transit surge is stopped by the arterial occluding wrist cuff the rate of flow into the forearm tissues was 37 5 c.c 100 c.c /minute an increase of 48 per cent

This suggests that in the measurement of arterial flow the pre-resistance vessels of the arterial trunk are involved to a large extent in the flow of blood into the arm When these larger pre-resistance vessels are not obstructed the blood courses right through the forearm segment and by passes the smaller resistance vessels.

This thesis is supported by the findings and similar arguments of Kerslake [8] who when measuring blood flow in a forearm segment by the venous occlusion plethysmographic technique with the arm in the horizontal position was able to increase the flow into the tissues of the enclosed segment by applying a suprasystolic pressure to a wrist cuff below a forearm plethysmograph

7 SHAPE OF ARTERIAL FLOW RECORD It might be thought that there would be graded exponential increases in hinderance to flow of blood into the limb It would not be surprising therefore if the arterial flow record rose in a curvilinear fashion However this is not the case (Fig 1) The records show a linear increase in volume for several pulsations and then suddenly reach a horizontal plateau The first resistance is probably the only one involved in the initial flow and this continues to be the major resistance factor until the vasculature of the limb is refilled

8 HYSTERESIS The arterial flow technique involved the complete occlusion and compression of the brachial artery However it might be suggested that measurements which were made after the release of this occlusion could involve a hysteresis or lag in arterial distention The degree of distention of the vessel *after release* of the occluding cuff to a given pressure may not correspond to that when the same external pressure is applied from a zero value. The relationship of arterial flow to pressure (compression curves) was studied. In Case 1 the curve was drawn as described in Section 4. In the second experiment the curve was drawn from measurements made after the cuff pres-

Table II Average measurements from experiments on 4 young subjects

	Arterial flow		Refill volume	
	c.c./100 c.c./m	% of Control	c.c./100	% of Control
Maximal flow control	38 5	100 0	3 85	100 0
10 Massaging strokes	41 5	107 9	5 68	147 7
Subatmospheric compression	41 7	108 4	4 47	118 8

sure fell to zero and then with sudden reapplications of the pressure to the desired value When pressure is lowered to zero two or three pulsations at the zero flow rate may be recorded Sudden reapplication of the second cuff pressure then permits recording of arterial flow at this residual cuff pressure In normal subjects these two procedures produce compression curves relating pressure to flow which are not significantly different. It does not appear therefore that the final state of the artery is any different whether pressure is *applied* or *released* The linearity of the records also suggests that hysteresis of the vessel wall does not occur to any significant degree after the release of pressure.

9 INFLUENCE OF TEMPERATURE ON MAXIMAL FLOW Two arterial compression curves from the same subject are presented in Fig 4 The upper curve was obtained by using a water bath at 44°C whereas the lower curve was obtained at 34°C

It will be observed that the maximum flow value obtained when the arm was heated was 48.4 c.c 100 c.c./minute whereas the flow value obtained with the cooler water bath was approximately 27 c.c 100 c.c /minute However when the collapsing parts of the compression curves were superimposed they followed the same trend to the point of cessation of flow The point at which the compression curve obtained from the heated limb commences to fall is at diastolic pressure and 18 mm. Hg lower than in the compression curve obtained with the cooled limb

The significance of this finding could best be examined by referring to a simple model that consists of a box in which flow through a thin walled rubber tube can be obtained where pressures in the box outside the tube can be varied as desired so that a compression curve of the rubber tube can be obtained

If various resistance tubes are placed on the outflow side of the tube coming from this box, linear compression curves can be obtained for the tube inside the box. These curves, like those in Fig 4 would have a common trend and collapse completely at the same pressure However they would differ in that the external pressure at which the compression curve began to decline would vary The larger the bore of the resistance tube, the lower would be the external pressure required to start the fall in the compression curve Thus, where we have two tubes in series as in this model it is changes in the bore of the second tube that gives compression curves like those in Fig 4 By the same argument in the intact limb where there are two sets of vessels in series, it will be changes in the second of these—namely the resistance vessels—that will be responsible for the results described in Fig 4

It is suggested that the differences observed in the compression curves in Fig 4 are in line with the thesis that the resistance of the resistance vessels has been increased by the cooling but that the brachial artery is unaffected These results support the contention that the compression curve that is being drawn by this technique is on vessels which do not respond to cooling

Discussion

It is suggested that there are three main factors responsible for these large initial flow rates.

First vasodilatation is induced by heat.

Second the maneuvers of elevating the limb draining the veins, occluding the circulation and then bringing the limb into the dependent position create an underfilled state in the vascular system of the limb and a zero pressure in the arterial trunk. This can be shown by an examination of an intra-arterial record made from a normal subject during and after such maneuvers A needle in the radial artery gave a pressure of [illegible] 32

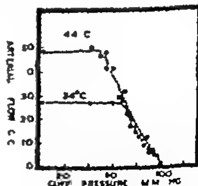


Fig 4 Two arterial compression curves from the same subject recorded 1 different temperatures

mm. Hg in the arm held vertically elevated. A cuff pressure of 280 mm. Hg was then applied. When the limb was then placed in the horizontal position the pressure in the artery fell to 2 mm Hg After such maneuvers and release in the fourth stage, the blood stream surges into the almost collapsed vessels, which present minimal resistance to flow This can be seen by examining the manner in which the intra arterial pressure returns to normal. After occlusion of the circulation in the limb for 50 seconds, release of the occluding cuff resulted in a rise to only 83/55 mm Hg, and then 20 seconds were necessary for a return to the pre-occlusion level of 122/74 mm Hg This systolic value of [illegible] mm. Hg immediately after release of the cuff a value which was 40 mm. Hg below the normal and which was associated with a rapid inflow rate, demonstrates the fall in pressure along the main arterial trunk during high rates of blood flow It is interesting to note that the initial rise in pressure in the artery after release of the obstructing cuff took one fifth of a second. It is suggested that this is the time involved in the refilling of the emptied and probably partially collapsed arterial tree. Similar measurements were made by Wallace and Stead[9] who found a fall in mean radial arterial pressure of 25 mm Hg during the high rates of flow after a period of 9 5 minutes of ischemia.

The zero intravascular pressure which is obtained in this method prior to release of the cuff may have an additional effect Bayliss[12] and Folkow[13] demonstrated that a fall in intravascular pressure is accompanied by a loss of tone in the resistance vessels. It is unlikely that this mechanism operates in the presence of vasodilatation due to heat.

Third the placing of the limb in the dependent and vertical position is important. The additional hydrostatic pressure assists in producing a maximal flow and the vessels are i l ne with and the flow is assisted by the force of gravity It will be noted in Fig 1 that when an arterial flow record was made with the limb placed in a plethysmograph held in the horizontal position the flow value obtained was 25 1 c.c./100 c.c minute, as compared with 42.3 c.c. 100 c. minute

of the preceding arterial flow record when the limb was vertical and dependent.

The experimental analysis of the question whether an arterial flow phenomenon is being obtained is borne out by the comparability of the flow values in vitro and in vivo shown in Section 2. The lack of response of the vessels to exercise and ischemia might be due to two factors either the resistance vessels are so dilated that the less responsive arterial trunk is the only vessel left causing resistance to flow or the dilatation of the vessels is maximal to the point at which no further dilator response can be obtained

The coincidence of the first point of collapse in the compression curve with the diastolic pressure is significant. If there were a nozzle of resistance vessels impeding flow then the point of initial collapse would be at a higher residual cuff pressure than the diastolic value

Lewis and Grant,[4] in their study of reactive hyperemia, occluded the circulation of the limb for periods up to 15 minutes, at the end of which time the cuff pressures on the limb were allowed to fall from the occluding pressure of 350 mm. Hg to 70 mm Hg The initial change in limb volume was used to calculate the rate of flow of blood into the limb. High values of 50 to 70 c.c./100 c.c./minute were recorded. It is likely that after these lengthy periods of occlusion the resistance vessels were so toneless that the main resistance met with during the initial inflow was that of the larger vessels in the arterial trunk. It is likely therefore, that under these conditions, arterial flow was being measured.

It has not always been defined in plethysmographic studies of the changes in resistance to blood flow which part of the vascular system (i.e. arteries or arterioles, or capillaries, etc) is most involved However Landowne and Katz[8] attempted to remove the influence of the resistance vessels by heat and ischemia, and the maximal flows obtained as a result of these procedures were thought to be more dependent on the cross-sectional area of the central arteries than on that of the other vessels. The prolonged ischemia used by these authors, as well as that used by

and Pickering[13] would make repeated observations difficult and uncomfortable if not dangerous, for subjects with impaired circulation in the limbs. This is avoided in the method described here.

It is interesting in this respect to compare measurements made by the venous occlusion plethysmographic technique with measurements made by the arterial flow method described here after 8 to 10 minutes of ischemia. There is a marked increase in the flow of blood measured by venous occlusion plethysmography but it does not reach the values of the arterial flow measurements after the same period of ischemia.

Summary

A technique is described for the production of maximal blood flow in the arm. The principle of the technique is to employ a maneuver which removes the resistance to flow of the resistance vessels. This is achieved by gravitational drainage of the vessels, and heat. The initial rate of flow into the limb is measured after the release of a suprasystolic tourniquet while the limb is in the dependent vertical position. It is suggested that this arterial flow rate is dependent mainly on the resistance to flow in the arterial trunk. Various experimental procedures were utilized to examine and support this thesis.

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Demonstration of the in vivo compressibility of the brachial artery in man

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There does not appear to be a successful technique for the demonstration of the resistance to compression offered by the brachial arteries whereby a curve of compression can be drawn Therefore it was considered to be worth while to attempt to devise such a technique and to apply it to groups of young and aged subjects.

The basis of the technique was to examine the manner in which the brachial artery collapsed when exposed to various external pneumatic cuff pressures. The degree of collapse of the brachial artery was observed by measuring the arterial blood flow by the technique of Mackay which is fully described by Mackay and Walker

Results

Measurements were made on 6 normal young subjects (29 2 ± 13 1 years of age) in whom palpation revealed no evidence of arteriosclerosis and on 17 elderly subjects with an average age of 78 4 ± 5.8 years, in whom the brachial artery was palpably hardened to varying degrees

In order to illustrate our findings compression curves from single experiments on 2 subjects are shown in Fig 1A The upper curve is from a normal 18 year-old subject (blood pressure 95 50 mm Hg) and the lower curve is from an 89-year-old subject (blood pressure 130 78 mm Hg) whose arteries were palpably hardened

Curves obtained from different subjects are sometimes difficult to compare since the pulse pressure and arterial flow rates vary from one subject to another Therefore an attempt was made to provide some basis for comparison by treating the data as follows

Rates of blood flow (see Fig 1B) were calculated as a percentage of the control blood flow values (i.e. the arterial blood flow values obtained when the pressure cuff was released to zero) These flow rates were plotted against the "cuff pressure value, which was calculated by subtracting the diastolic pressure from the residual cuff pressure at which the flow was recorded This difference was then expressed as a percentage of the pulse pressure The compression curves in Fig 1A were calculated and plotted in this manner and are shown in Fig 1B Thus the blood flow expressed as a percentage of the control flow is plotted against the supradiastolic value of the cuff pressure as a percentage of the pulse pressure This treatment was applied to the compression curves of the young and elderly subjects. The results are presented in Fig 2

These results show that in the young

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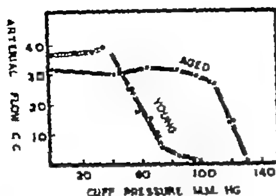


Fig. 1A. Compression curves plotted for young subject (18 years old blood pressure 95/50 mm. Hg) and an elderly subject (blood pressure 130/78 mm. Hg). The "arterial" flow vertical ordinate, is measured in cubic centimeters per 100 c.c. of limb volume per minute.

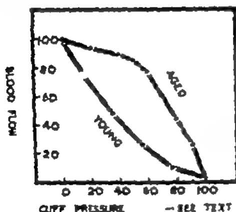


Fig. 1B. These curves are calculated and plotted from those in Fig. 1A. The "blood flow" is the percentage of the flow measured of the zero control flow. The "cuff pressure" is the percentage of the supradiastolic value of the cuff pressure of the pulse pressure (*see text*).

the compression curve has a concavity facing upward whereas in the aged subjects it has a concavity facing downward. However there were 2 additional elderly subjects in whom after the first decline the curve took a concave trend facing upward and then a concave trend facing downward before reaching the zero flow level.

The relationship of the initial point of decline of the compression curve to the diastolic pressure was measured by the indirect auscultatory method at the point of cessation of sounds (fourth to fifth stage. In the young and the elderly subjects the mean points of initial compression were 3.67 ± 4.4 and 0.41 ± 7.0 mm Hg respectively below the auscultatory diastolic point.

In vitro studies on the relationship of external pressure to collapse of an artery. In order to obtain a better understanding of the results described in the studies in vivo we thought that it would be of value to carry out a study in vitro.

An attempt was made to mimic the in vivo method by perfusing a segment of an artery with saline at a steady pressure and flow. A 10-cm. length of femoral artery was dissected from fresh postmortem material. Flow through the vessel was measured at various external pressures and thus it was possible to plot a compression curve.

One of the problems of the in vivo study is the nature and contour of the pressure pulse wave, and one should consider whether this factor might be decisive in producing the shape of the compression curves in Fig. 1. We considered therefore that it would be of interest to see what happened when this factor was eliminated by using nonpulsatile steady flow in an in vitro experiment.

The resistance to compression offered by isolated arteries has been studied by various authors using both pressure-volume and pressure-flow methods. By perfusing isolated arterial segments, Janeway and Park[4] found that an excess pressure of 3 mm. Hg was required to prevent flow through a normal artery, atheroma had little effect but calcification raised to 27

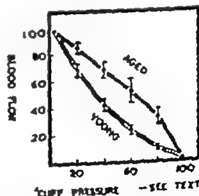


Fig. 2. These compression curves were plotted from a series of 6 young subjects (average age of 29.2 ± 13.1 years) and 17 elderly subjects (average age of 84 ± 5.8 years). They were plotted as those in Fig. 1B.

mm Hg the excess external pressure required to prevent flow. Eldahl using a pressure volume method showed that 10 mm. Hg of excess external pressure was required to completely collapse normal vessels, and 20 mm. Hg was required for sclerosed vessels. Roach and Burton using a similar volume technique found that a negative intraluminal pressure of 30 mm. Hg collapsed normal vessels and that as much as 60 mm. Hg was needed for the iliac arteries of old people.

Two in vitro techniques were devised in order to study the relationship of external pressure to the manner of collapse of the isolated artery. (1) The first of these attempted to mimic the above-described in vivo experiment in which flow rate was used to measure the degree and manner of collapse of the vessel. (2) The second approach examined the changes in volume of an isolated segment of an artery at various transmural pressures.

FIRST TECHNIQUE.

Apparatus. The basic elements of this apparatus were a saline-filled metal box with a Perspex lid in which the vessel was placed. The flow of saline through the isolated segment of artery was obtained from a reservoir of saline set at a height to give a lateral intravascular pressure of 85 mm. Hg; the resistance of the apparatus was one fourth that of the arteries. The pressure in the extravascular space was controlled with a reservoir set at a selected height to produce selected positive and negative transmural pressures.

Procedure. The measurements of flow were carried out at various extravascular pressures. To ensure that hysteresis was not involved, external pressures were increased and decreased in steps.

Thirteen experiments were carried out on normal and sclerotic arteries. Typical compression curves from a normal artery and a sclerotic artery are presented in Fig. 3. It will be noted that the normal artery tends to collapse in a linear fashion and compares favorably with the collapse curve of a thin elastic tube (straight dashed line in Fig. 3). The collapse curve of the sclerosed artery tends to be more curvilinear and its final collapse is 22 mm. Hg higher than the perfusing pressure. It is interesting to compare these results with those of the in vivo experiments in which some similarity in the shape of the collapse curves will be noted.

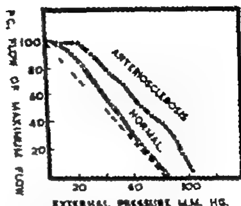


Fig. 3. These in-vitro compression curves were drawn by plotting flow against external pressure. Ten-centimeter lengths of human femoral arteries were used. The upper curve was plotted from a vessel that was diagnosed microscopically as being sclerosed. The lower curve was plotted from a normal vessel.

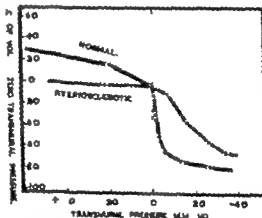


Fig. 4. These in-vitro compression curves were drawn by plotting volume against external pressure. The type of vessel is indicated.

SECOND TECHNIQUE. To obviate the possibility that the initial delay in collapse of the artery at the lower pressures was due to some defect or artefact in the method employed, the changes in the volume of the blood vessel at various transmural pressures were recorded.

Apparatus. This apparatus is basically much the same as that employed in the first technique. Added was an intravascular burette which recorded the volume and pressure inside the blood vessel. There was

also an extravascular saline manometer for recording the external pressure. The saline pressures were calibrated against a mercury manometer. By the application of pressure at the rate of 12 mm. Hg per second from a reservoir to the extravascular space, the pressure in the extravascular space was permitted to rise in a steady linear fashion. The shadows of the manometer levels were recorded on a moving photographic film. Changes in the extravascular and intravascular levels of the saline are also recorded. The point at which the shadow of the level in the extravascular saline manometer crosses that of the intravascular saline level is the point at which the transmural pressure can be said to be zero. The procedure of the second technique was carried out after the application of the first technique to the vessel. Curves are presented in Fig. 4 from two typical experiments, one from a normal vessel and one from a sclerosed vessel.

That part of the curve to the right of the vertical line which was produced with negative transmural pressures could be described as a compression curve. Here the sclerosed vessel, as compared with the normal, again demonstrates an initial resistance to compression, which finding supports the suggestion that the delay in collapse of the initial part of the compression curve is probably not an artefact of the first in vivo technique.

When the transmural pressures are positive (left of the vertical dashed line), the normal blood vessel increases in volume with increasing positive transmural pressures, whereas the sclerosed vessel is less distensible.

The change from negative to positive transmural pressure causes an abrupt change in the volume of the segment of the normal vessel; this effect is more gradual in the sclerotic vessel.

Eleven normal and two arteriosclerotic arteries were examined by these in vitro methods. The mean excess external over perfusion pressure at which flow ceased was 5.5 ± 2.1 mm. Hg for the normal vessels and 20 and 22 mm. Hg for the two arteriosclerotic arteries. From the pressure volume curves, the mean external pressure at the point at which the major volume of fluid was expressed from the normal vessels was 8.25 ± 0.98 mm. Hg higher than zero transmural pressure. The mean excess external pressure at which re-expansion began was 5.14 ± 1.95 mm. Hg above zero transmural pressure.

For the arteriosclerotic vessels, the excess external pressures at which the major contents were expressed were 23.5 and 25 mm. Hg, and re-expansion occurred 20 and 18 mm. Hg above zero transmural pressure.

Discussion

There are three stages that might be considered in examining and comparing the in vivo arterial compression curves in the young and elderly subjects.

Stage I, that part of the compression curve where the residual cuff pressures rise from zero to diastolic pressures and where usually a plateau of the flow values is obtained. Here there does not appear to be any significant difference.

The possible explanation for a plateau in this part of the compression curve is the relative indistensibility of the blood vessel wall at the positive transmural pressures that result from applying cuff pressures up to the diastolic values. This lack of distensibility was demonstrated in the in vitro experiments in Fig. 4. Thus, when the cuff pressure is zero, the internal transmural pressure will in vivo normally fluctuate from 70 to 120 mm. Hg. Over this range of pressures there will be little change in the caliber of the blood vessel. If the artery had the elastance of a thin-walled rubber tube, then this first part of the compression curve would be different in that it would proceed to collapse with the first application of pressure (see dashed line, Fig. 3).

One of the factors which may influence the nature of the first part of the collapse curve in studies on human beings is that the shape of this part of the compression curve may be masked by the hindrance to flow in their resistance vessels. The compression curves drawn from changes in volume recorded in the in vitro studies were not affected by this resistance phenomenon, and since the collapse curves are similar in shape to those of the in vivo flow studies, this adds support to the suggestion that the in vivo arterial blood

flow phenomenon is not affected by the resistance vessels.

Stage II: that part of the compression curve where the cuff pressure rises above the diastolic value. The probable explanation of the difference here is that there is a factor resisting collapse in the sclerotic vessel wall. It may be that here in this stage will be found the most significant difference indicating the physical changes in the blood vessel wall.

Stage III: the final part of the compression curve. Account should be taken of the shape of the pressure pulse, which is different in young and elderly subjects.

The pressure pulse peak in elderly subjects is wider and more rounded than the normal; thus, when a pressure cuff is applied at the peak of the pressure curve, it will, over a given range of pressures, close more abruptly in the sclerotic than in the normal vessel. This may be the explanation of the abrupt fall in Stage III to the zero flow line of the compression curve in subjects with sclerotic arteries (Fig. 3).

The similarity of shape of the compression curves in the in vivo pulsatile and in vitro steady flow studies will support the suggestion that changes in the mechanical properties of the vessel wall with age may play a significant part in these findings.

Summary

The technique of Mackay and Walker[3] for drawing in vivo compression curves of the brachial artery was applied to a group of 6 young subjects (average age 29.2 years) and 17 elderly subjects (average age 78 years). The compression curve over the diastolic to systolic range in the normal subject has a concavity facing upward when flow (vertical ordinate) is plotted against pressure. In elderly subjects the curve has a convexity facing upward. Studies of isolated arterial segments confirmed the in vivo findings and supported the suggestion that an important factor involved is the physical change that occurs in the blood vessel with aging.

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Effects of acute coronary occlusion on performance of right and left ventricles in intact unanesthetized dogs

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Acute coronary occlusion is generally recognized clinically in terms of characteristic signs, symptoms and electrocardiographic patterns which are only vaguely related to the capacity of the heart to pump blood. Changes in ventricular pressure or outflow are rarely measured in patients during acute heart attacks. Information of this sort can be obtained during experimental coronary occlusion of exposed hearts in anesthetized dogs, but the base lines of function and the control mechanisms are distorted. Techniques have been developed recently by which the performance of the ventricles can be described continuously in terms of some 12 simultaneous physical variables with generally accepted definitions and units.[1] Indwelling ultrasonic flow transducers and pressure cannulas are used to record fundamental variables and analogue computers are employed to derive 10 additional pertinent variables. The performance of each ventricle as a pump is thus recorded continuously during spontaneous and experimental responses in healthy active dogs. Techniques have been developed for acutely occluding a major coronary artery in such preparations; little or no evidence of discomfort was observed.

Methods

In dogs which weighed from 20 to 25 kilograms, pulsed ultrasonic flowmeter transducers were chronically implanted on the main pulmonary artery and the root of the aorta, in order to record the instantaneous volume flow from both ventricles.[1] A single molded band of acrylic encircled and conformed to the walls of the aorta and pulmonary artery; this band had been cast in a mold constructed from plastic injections of these vessels in situ. Two sets of barium titanate crystals were embedded in it and properly aligned to sample the flow across the two vessels (Fig. 1). The wave forms of normal aortic and pulmonary flow are illustrated schematically in Fig. 1 to indicate the characteristic differences between the ejection patterns of the left and the right ventricle. The left ventricular outflow attains peak velocity very early in systole and decelerates during the major portion of the

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systolic interval. A sharp retrograde surge of blood accompanies closure of the aortic valve at the end of systole. In contrast right ventricular ejection begins before left ventricular outflow and rises more gradually to a peak in mid-systole con tinues longer and ends in a slower retrograde surge Since both arteries were confined within the single orifice of the flow section expansion of the cross-

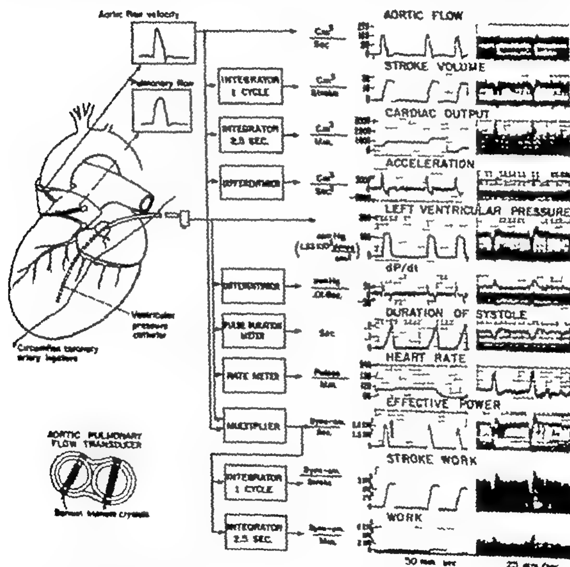


Fig 1 Left ventricular performance in ph sical terms, derived continuously by analogue computer Insta taneous olume was ecorded by pulsed ultrasonic flowmeter encircling the aorta and pulmonary rteries hich as later calibra ed directl in terms of olume flow (cm sec) in sit Additional ariables from single aortic flowmeter ere der ed by analogue computers Stroke olume was derived by integrating aortic flow over 2 3 seconds and adjusting he scale to read as cm /minute Acceleration of aortic flow was obtained by continuously registering function of the slope of the aortic flow curv by means of differentiating circuit. Left entricular pressure as recorded directly nd the rate of change of pressure was derived through differentiating circuit Duration of systole was indicated by ramp voltage ascending constant slope during the interval hat en ricular pressure exceeded bout 10 mm Hg. Effecti instantaneous power w the continuous product of aortic flow times entricular pressure nd indicates the te of doing work. Stroke work and accumulated work were derived from the power record by integrating it over each stroke nd over 2.5 seconds, respectively

sectional area of the aorta during systole could occur at the expense of the pul monary arterial lumen Expansion of un confined systemic arteries is slight but not negligible ; ranging up to 11 per cent in the cross-sectional area of the human aorta.[4] Counterpressure by the pulmonary artery should diminish this source of artifact to some extent. Flow in the coronary artery does not pass through the aortic flowmeter channel and is not in cluded in the recorded deflections.

An indwelling cannula, extending from the left atrium through the posterior wall of the thorax, served as a guide for a catheter to be passed through the mitral valve ring to record left ventricular pressure by means of a miniature differential transformer pressure transducer Right ventricular pressure was recorded either through an indwelling cannula which extended to the outside from within the infundibulum or by cardiac catheterization through the jugular vein exposed under local anesthetic

Additional pertinent information in re gard to the function of the two ventricles was derived by means of analogue com puting techniques previously described in detail These analogue computers con tinuously describe left ventricular func tion in terms of 9 variables with standard physical units, derived from left ventricular pressure and aortic flow The calibration scales in Fig 1 illustrate the magnitude of the fluctuations in a representative example from a dog which weighed 22 kilograms. The same information was derived f om pulmonary arterial flow and right ventricular pressure to provide a continuous description of the function of the right ventricle as well. Since the systolic pressure and peak ejection velocity are substantially lower for the right ven tricle than for the left the functions derived from these recordings are smaller

Abrupt occlusion of a major coronary artery was accompli hed in 9 animals by one of two different techniques In the first 3 animals a loop of nylon suture encircled either the left anterior descending or circumflex artery and passed throu h a length of polyethylene tubing which ex tended to a point just under the skin in the interscapular region Un ler local anesthetic the ends of the snare were retrieved Tension on the suture with coun terpressure on the polyethylene tubing produced complete occlusion of the artery but could be instantly released if the animal struggled or displayed evidence of discomfort (i.e. angina) In these experi ments the animals reclined quietly during coronary occlusion and did not appear to experience pain after the snare was tight ened In the last 6 animals a double over hand knot was tied in a heavy waxed nylon suture which encircled the left circumflex artery One end of the suture ex tended through the interscapular skin and the other end emerged from the fifth left intercostal space. These sites were chosen so that the suture was in an approxi mately straight line Under these condi tions, tension applied to the two ends of the suture occluded the coronary artery with minimal distortion or displacement of intrathoracic structures.

Since acute coronary occlusion rarely occurs spontaneously in patients with coronary arteries which are otherwise normal the anterior descending branch of the left coronary artery was generally ligated at the time of the original opera tion and the occlusive loop was installed on the circumflex coronary artery The relative positions of the ligature and snare in such an experiment are illustrated in the insert in Fig 4

Design of the experiment The experiment was designed originally to follow changes in the performance of the right and left ventricles before, during and after acute coronary occlusion Ventricular incompetence tends to show up under stress. Isopropylarterenol (Isuprel Winthrop) was injected intravenously to impose a load on the heart during the control period for comparison with the response to a similar injection after coronary occlusion In this series of experiments the occlusion of a single major coronary artery produced slight or negligible changes in performance Sudden occlusion of a second major coronary branch produced severe deficiencies in ventricular performance but the animals died suddenly within a few minutes or a few hours. Because severe but survivable myocard l infarction coul l not be in d iced this report will deal with the acut

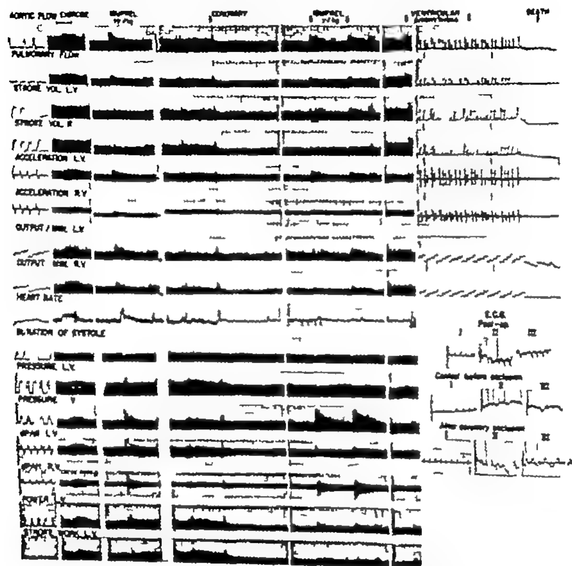


Fig 2 Continuous description of right and left ventricular performance by techniques indicated in Fig 1. The control records (*left*) at 25 mm./sec. show the wave forms of the different variables. The effects of exercise on treadmill at 4.5 m.p.h. on 5 per cent grade are presented for comparison with the response to isopropyl arterenol (Isuprel). The arrow on the *Coronary* record indicates time at which the circumflex coronary artery was abruptly occluded. The left anterior descending coronary artery had been ligated 6 days earlier at the time of operation.

effects of coronary occlusion in intact unanesthetized dogs which were lying quietly and lightly restrained.

Results

The changes in right and left ventricular performance were continuously recorded in terms of pressure and outflow with as many as 12 additional variables derived by analogue computers, as illustrated in Fig. 2. The first vertical row of records was inscribed at a paper speed of 25 mm. per second to illustrate the wave forms of the different recorded variables. The second row of records (paper speed of 0.25 mm. per second) represents a typical response to treadmill exercise at 4.5 miles per hour on a 5 per cent grade. The aortic and pulmonary flow velocities increased but the stroke volume remained unchanged because the duration of systole was reduced during the exertion. The increased cardiac

output was achieved by tachycardia The pressure rate of change of pressure and power and stroke work were increased in both ventricles.

Intravenous administration of Isuprel (1γ per kilogram) produced a load on the heart of the same general sort as exercise had but the response was of greater intensity and shorter duration

A ligature encircling the circumflex coronary artery was abruptly tightened at the arrow labeled *Coronary* in the fourth column of records (Fig 2) Although the animal continued to recline quietly without movement or signs of discomfort all the recorded variables, except duration of systole displayed a very large transient increase Electrocardiograms taken just after the coronary occlusion revealed a pronounced deviation of the S-T segment which was not present in the control period These changes in electrocardiographic pattern characteristic of myocardial ischemia persisted to the end of the experiment Immediately after the transient stimulation of ventricular performance pronounced depression appeared in all the recorded variables except the heart rate and the duration of systole The reduced stroke volume was partially compensated by the sustained elevation of heart rate The peak velocity of outflow from the right and left ventricles, acceleration of the blood through the arteries, right and left ventricular pressure rate of change of pressure and ventricular power and stroke work were all depressed after occlusion of the circumflex artery Administration of Isuprel after the coronary occlusion produced changes which were similar to the control response although they began from different base line conditions. The magnitude of the tachycardia was considerably reduced Left ventricular systolic pressure diminished whereas right ventricular systolic pressure increased

Shortly after the second administration of Isuprel ventricular arrhythmia developed for about 1 minute owing to a series of premature ventricular systoles. About 10 minutes later another sequence of premature contractions appeared and this time the heart abruptly ceased functioning a a pump Although electrocardiograms were not obtained during this phase of the experiment death was attributed to ventricular fibrillation The terminal events are displayed at fast paper speed (10 mm. per second) and demonstrate that the last recognizable ventricular contraction was a premature ventricular systole (see the right hand panel in Fig 2)

Postmortem examination disclosed minor pleural and pericardial adhesions along the incisions cannulas, and wires in the thorax The left anterior descending and circumflex arteries were completely occluded at the sites of the two ligatures. The myocardium along the distribution of these arteries was discolored and both ventricles and the right atrium were grossly distended

In another experiment the anterior descending artery was ligated at the time of the aseptic operation the resulting S-T T deformity persisted until the experiment was conducted (see Lead II on the left side of Fig 3) The response to the intravenous administration of Isuprel was similar to that in Fig 2 However acute occlusion of the circumflex coronary artery was followed by a prompt decline in pulmonary and aortic flow accumulated stroke volume (cardiac output) right ventricular power and accumulated stroke work. Right ventricular systolic and diastolic pressures were grossly elevated About 1 minute later the first of a series of premature ventricular contractions produced progressively more severe arrhythmia until the animal whined stiffened and died abruptly In this instance, the abrupt transition from frequent premature ventricular contractions to the gross arrhythmia of ventricular fibrillation was recorded on the electrocardiogram (at the bottom of Fig 3) After a few seconds the fibrillation slowed but the heart failed to recover rhythmic contractions.

Profound changes in ventricular performance were observed in another dog in which the anterior descending coronary artery was ligated at the time of operation and the circumflex coronary artery was suddenly occluded during the recordings illustrated in Fig 4 A sustained tachycardia effectively compensated for the reduced velocity of aortic and pulmonary flow and stroke volume Left ventricular systolic pressure was reduced wherea the

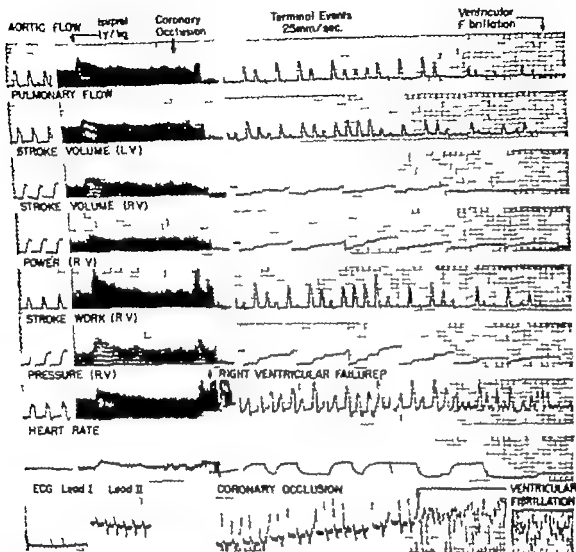


Fig. 3. Changes in ventricular performance after sudden occlusion of the circumflex coronary artery. The left anterior descending coronary had been ligated previously. Intrapleural pressure was applied to the back of the pressure gauge to record effective right ventricular pressure in this experiment. Note the pronounced elevation of effective right ventricular pressure, both systolic and diastolic, after coronary occlusion.

diastolic pressure was visibly elevated. During the response to Isuprel after coronary occlusion, the ventricular systolic pressure was diminished, in contrast to its elevation by this drug during the control period. These extreme changes in ventricular function were accompanied by insignificant changes in the electrocardiographic patterns (Lead II) at the lower right of Fig. 4. No evidence of discomfort resulted from tightening of the coronary ligature.

The reduction in ventricular ejection velocity was accompanied by a characteristic change in the wave form of aortic flow. Normally, the velocity of aortic flow reaches a peak early in systole. Flow decelerates during the remainder of the systolic interval. This phenomenon is confirmed in early peak acceleration in the records (see Fig. 1). In contrast, pulmonary flow accelerates more slowly and reaches a peak in mid-systole. After coronary occlusion, the aortic flow reaches peak values nearer mid-systole, so that the pattern of left ventricular ejection comes to resemble that of normal right ventricular outflow (see insert in Fig. 1). The reduced left ventric

ular capacity for accelerating blood to high velocity in the aorta may be a fundamental functional defect which results from the experimental coronary occlusion (see *Limitations* below)

Limitations of the experiment

Experimental coronary occlusion in dogs was studied as a model of spontaneous coronary obstruction in patients. The validity of this model requires confirmation by recording pertinent variables in patients under corresponding clinical conditions. Diffuse atherosclerosis of the coronary arteries is a common feature in patients with acute coronary occlusion Canine coronary arteries are generally free of atherosclerosis or local narrowing that might stimulate the production of collaterals. The high incidence of ventricular arrhythmia and ventricular fibrillation may be related to the abrupt ischemia produced in the absence of collateral supply The previous ligation of the left anterior descending coronary artery was designed to simulate more accurately acute coronary occlusion superimposed on some degree of coronary insufficiency The results of these experiments should not be extrapolated to human coronary occlusion without validation by direct measurements on patients. If these experiments stimulate interest in making such studies or suggest hypotheses that can be tested in patients, the effort will have been worth while

The combined aortic-pulmonary flow transducer was developed because it almost completely eliminated spontaneous rupture of the aorta previously rupture had followed by about 10 days the installation of a single plastic flow section on the aorta in about 10 to 25 per cent of our chronic preparations. It also eliminated the necessity of dissecting between the aorta and pulmonary trunks to install two individual transducers. The lumina of the aorta and pulmonary artery were not constricted by the double flow section or by the growth of connective tissue within it. Since adhesions failed to form slight movement of the flow sections which may produce artifactual fluctuations on the record could occur during the cardiac cycle The lack of adhesions also interfered with calibration of the gauges in situ at the end of the experiment. When the arterial pressure fell the arterial walls pulled away from the flowmeter crystals.* Although data for electronic calibration of the flowmeters were readily available, these have not yet been regarded as sufficiently reliable without confirmation by direct volumetric calibrations. The data in this report are intended as a qualitative description of some acute effects of coronary occlusions in conscious dogs, in order to permit exploration of the changes in the mechanical properties of the ventricles as pumping chambers

Extrapolation

The most dramatic effect of acute coronary occlusion in this study was the frequent development of ventricular arrhythmia which terminated in fatal fibrillation Disturbances in the process of myocardial excitation are of great clinical and theoretical importance, but do not contribute greatly to our understanding of the changes made in the mechanical capabilities of the heart by myocardial ischemia.

The right and the left ventricles are very different with respect to the structure and configuration of their chambers, their coronary supply and the kind of vascular bed into which they eject. In spite of these important differences the output of the two ventricles is balanced with remarkable precision [3] An imbalance in the output of the two ventricles must result in a transfer of blood from one circuit to the other Both circuits receive branches from the left anterior descending and circumflex arteries, but the distribution of the blood to the myocardial walls of these two chambers must be unequal Occlusion of a major coronary artery should have a more serious effect on one ventricle than on the other Within the limits of the experimental methods employed such imbalance in the output of the two ventricles could not be identified In one animal right ventricular systolic and diastolic pressures were promptly elevated to very high levels during the brief interval between occlusion and fibrillation (see Fig 3) This phe

*Since this study was completed, firm adhesion of the plastic flow section to the aorta and pulmonary artery has been achieved by sprinkling powdered Gelfoam on the inner and outer surfaces of the flow section.

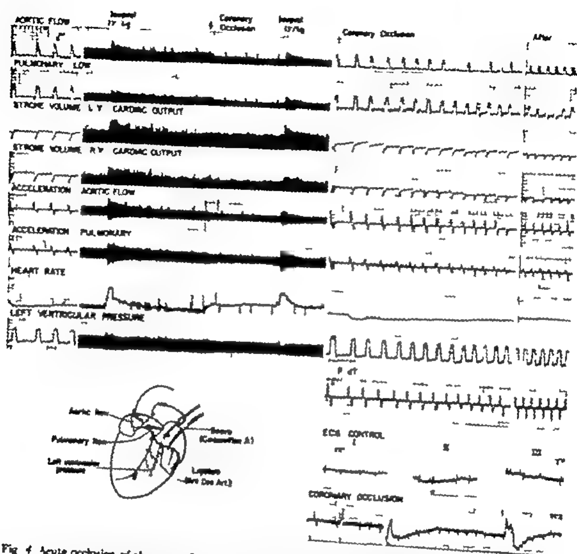
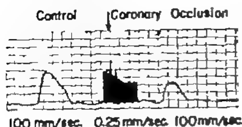


Fig. 4. Acute occlusion of the circumflex coronary artery (anterior descending artery previously ligated) produced prompt reduction in pulmonary artery and aortic flow velocity and acceleration of flow. The center panel shows the right and left ventricular outputs, obtained by integrating aortic and pulmonary flow over 2.5-second intervals. Reduced stroke volume was offset by sustained tachycardia, maintaining cardiac output. Changes in left ventricular ejection patterns are illustrated by records on the right (paper speed 25 mm./sec.).

nomenon might signal imbalance of ventricular competence with the right ventricle pumping excess blood into the lungs. This phenomenon was not observed in any other experiment in the series. Of greater significance was the consistent change in the pattern of left ventricular ejection after coronary occlusion.

The left ventricle as an impulse generator. Left ventricular ejection is commonly visualized as a squeezing or wringing action sustained during the systolic interval. Spencer and Greiss[8] directed attention to the fact that the velocity of aortic flow rapidly attains a high peak during the first part of systole. Ejection velocity slows down during the remainder of systole (see Fig. 1). In other words, the rapid acceleration of blood through the root of the aorta at the onset of systole is promptly followed by deceleration of the flow during most of the systolic interval (see acceleration record in Fig. 1). The right ventricle serves a low-resistance low-pressure pulmonary circuit and attains a peak velocity of outflow in mid-systole (see Figs.

LEFT VENTRICULAR EJECTION VELOCITY



RIGHT VENTRICULAR EJECTION VELOCITY



Fig 5 Left entricular ejection elocity is illustrated before nd soon fter occlusion of the circumflex coronary rtery t demonstrat the slower accelera tion t peak elocit near mid-systole Right entricular jection elocit also rises more slowly to lower peak alue after the coronary occlusion.

2) The left ventricle pumps like an impulse generator suddenly imparting a large amount of energy to the blood in the ventricle so that it rapidly attains a high velocity of outflow and continues to flow out through the aorta by its inertia. In studies on isolated strips, myocardium has been shown to develop maximum tension during isometric contraction and to lose contractile tension during shortening The reduction in contractile tension is determined by the rate and amount of shortening

Since the left ventricular myocardium delivers very large force in a very brief time it develops a high impulse (impulse = force × time) like advancement of a piston by striking it with a hammer In contrast the right ventricle normally ejects blood more gradually like a piston advanced by a rotating drive shaft. Unlike their mechanical counterparts the ventricles can change their ejection characteristics. When pulmonary vascular resistance is increased (e g by atelectasis hydrothorax) the pattern of right ventricular ejection into this high resistance system closely resembles the pattern of normal left ventricular outflow

Sudden obstruction of a major coronary artery characteristically produces the following changes in the pattern of left ventricular ejection the ventricular pressure rises more slowly the velocity of aortic flow increases more gradually to a peak level near mid-systole peak acceleration of the blood is reduced (Fig 5) Systolic left ventricular pressure is usually lower The sequence of these changes is apparent in the high-speed records on the right side of Figs. 3 and 4 Right ventricular flow velocity stroke volume and acceleration were also reduced but without much change in wave form It is tempting to speculate that abrupt coronary occlusion leads to rapid inactivation of a portion of the left ventricular wall which then bulges and does not contribute to ventricular ejection The contracting myocardium must shorten more than normally to elevate pressure in the left ventricular chamber This process is reminiscent of early right ventricular ejection At the onset of systole the inflow tract of the right ventricle is believed to contract first, distending the outflow tract or conus region[7,8] This postulate is worth further study as a mechanism for the changes observed in left ventricular ejection after coronary occlusion

Summary

Changes in the mechanical performance of the right and left ventricles were studied before during and after abrupt occlusion of a major coronary artery by directly recording from indwelling pressure cannulas and flowmeters. Analogue computers were used to derive additional pertinent variables, so that an engineering type of description of ventricular function was inscribed in as many as 22 variables with standard physical units. In 7 of the 9 animals in the series the anterior descending coronary artery was ligated at the time of operation days or weeks before the experiment. The principal effects of acute occlusion of the left circumflex coronary artery in unanesthetized dogs were a reduction in peak ejection velocity peak acceleration and stroke volume of the left ventricle These changes may be

attributed to interference with the left ventricle as an impulse generator since the pattern of ejection assumed some of the characteristics of the pattern of normal right ventricular outflow. Sustained tachycardia compensated for the reduction in the stroke volume so that cardiac output was well maintained. The experiments in which large changes in left ventricular performance occurred were suddenly terminated by ventricular fibrillation within minutes or hours of the experimental coronary occlusion.

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Case reports

Isolated congenital pulmonary valve incompetence

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Pulmonary incompetence secondary to severe pulmonary hypertension is not uncommon A recent report drew attention to the frequency of pulmonary incompetence after radical surgery for pulmonary stenosis. Pulmonary incompetence may follow rheumatic carditis bacterial endocarditis or syphilis. Isolated congenital pulmonary incompetence is rare Abbott[1] found 8 examples in 1 000 cases of congenital heart disease. Ongley and associates[2] commented on the clinical findings in 6 patients seen over a period of 5 years and Collins and associates[3] discussed the case of a patient in whom the diagnosis was made by cardiac catheterization and direct angiocardiography Both of these papers draw attention to the presence of identical pressures in the pulmonary artery and right ventricle. Collins and associates[3] confirmed the diagnosis by demonstrating the reflux of contrast medium from the pulmonary artery into the right ventricle after a selective injection into the pulmonary artery In 3 patients who were studied at The Children s Medical Center in Boston[7] the condition was considered to be innocuous and did not require any treatment

It is our purpose to present the case of a patient in whom the diagnosis was made clinically and later confirmed by catheterization of the right side of the heart cineangiocardiography and intracardiac phonocardiography

Case report

A J C (Unit number 246809), a 23-year-old married woma was referred because of the presence of a cardiac murm r The murmu was first heard when the patient was 5 years old She had no symptoms of cardiac disease and had undergone t o normal pregnancies.

The patient had attended nother hospital hen she wa 16 years old 7 years before she referred t us. At that time a linical diagnosis of pulmonary incompetence had been made This information not available when the patient a first seen by u some 3 month after the birth of her second hild. There wa no past history of heumatic fever horea or bacterial endocarditis.

The patient had 5 siblings 4 of whom were ell nd had been examined nd were found t be normal The fifth sibling had been rejected for military service because of heart murmur H as examined nd found t have small ventricular septal defect but no evidence of a lesion of the pulmonary alve

On physical examination the patient looked ell. The abnormal findings were confined to the cardiovascula system. The peripheral pulses were normal nd regular The systemic blood pressure w 105/75 mm. Hg The venous pressure i the neck wa not elevated. I particular no dominant w detected. There was isible pulsation in the second left i tercostal space The pex be t w hyperdynamic right entricular in type nd situ ted t the mid-clavicular line There as marked right ventricular lift at the left ternal edge On palpation a sy tolic and diastolic thrill could be felt in the pulmonary area. On percu ion ther as

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increased dullness in the second left intercostal space. On auscultation at the pulmonary area the first sound was normal and was followed by a loud ejection sound. The two components of the second sound were heard. Closure of the pulmonary valve was accentuated and did not appear to vary significantly during quiet respiration. A phonocardiogram confirmed that closure of the pulmonary valve occurred from 0.06 to 0.08 second after closure of the aortic valve, with slight but normal respiratory variation. The ejection sound preceded an ejection type of systolic murmur (Grade 3 out of 4) which was best heard in the pulmonary area but which was well conducted to the neck and to the bases of both lungs posteriorly. Closure of the pulmonary valve was followed by a loud, long Grade 4 (out of 4) medium-frequency diastolic murmur which was heard best at the second and third intercostal spaces close to the sternal edge. The murmur was conducted widely over the precordium. It was noted that at the lower end of the sternum the diastolic murmur was of lower frequency and became louder and longer on inspiration. No third sound was heard. The lungs were clear and there was no clinical evidence of heart failure. Examination of the blood revealed a hemoglobin of 12.4 Gm. per 100 ml. with a packed cell volume of 38 per cent. Blood Wassermann and Kahn tests were both negative.

X-ray examination revealed a heart of normal size. There was marked dilatation of the main pulmonary artery and its main branches (Fig. 1). There was no pulmonary plethora, and the peripheral lung fields were clear. On x-ray screening the pulmonary artery pulsations were greatly increased; however there was no hilar dance. The electrocardiogram demonstrated sinus rhythm with right axis deviation and evidence of right ventricular hypertrophy (Fig. 2).

The physical working capacity was measured and found to be in the normal range. The heart rate was 170 per minute with the patient walking on

Table I

Site	*Blood oxygen saturation* (%)	*Pressure (mm. Hg)*	
		Systolic/ Diastolic	*Mean*
Main pulmonary artery	68 69 71	24/0	10
Mid right ventricle	69	30/0–4	—
Low right ventricle	67		
Mid right atrium	69	= 2	1
	65	= 0	
High right atrium	69		
Low superior vena cava	67		
Mid superior vena cava	67		
High superior vena cava	66		



Fig. 1. Posteroanterior x-ray film of chest.

motor-driven treadmill at 6.2 kilometers per hour up a 5-degree slope. (Normal values for a female in our department are 6.3 ± 0.78 km. per hour.)

A clinical diagnosis of idiopathic pulmonary incompetence was made.

When the right side of the heart was catheterized the pulmonary arterial pressure was found to be 24/0 mm. Hg (Fig. 3). When the catheter was withdrawn into the right ventricle, the diastolic pressure was found to be similar to that in the pulmonary artery (Fig. 4). There was a systolic gradient of 6 mm. Hg across the pulmonary valve. Serial samples of blood did not show any evidence of a left-to-right shunt (Table I).

Selective cineangiocardiography was performed by injecting 40 ml. of 76 per cent Urografin into the pulmonary artery during diastole. The injection was triggered using a timing device linked to the R wave of the electrocardiogram. A No. 8F N I H angiography catheter was used for the rapid injection which was completed in 0.8 second using a Royal Melbourne Hospital type of compressed-air power syringe. Films were taken at 48 frames a second with the patient in the left lateral position. Considerable regurgitation of contrast medium from the dilated main pulmonary artery into the dilated right ventricle occurred in diastole (Fig. 5). Normally no contrast medium will reflux into the right ventricle when contrast is injected distal to the pulmonary valve. Therefore, the cineangiocardiogram confirmed the clinical diagnosis of pulmonary regurgitation. A phonocatheter size 8F was positioned in the main pulmonary artery. A loud ejection type of systolic murmur was heard and recorded. After closure of the pulmonary valve there was a medium-frequency diastolic murmur (Fig. 6). When the tip of the catheter was withdrawn to the body of the right ventricle, the systolic murmur became less loud

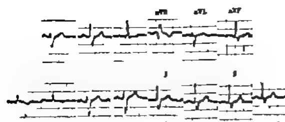


Fig. 2. Electrocardiogram.

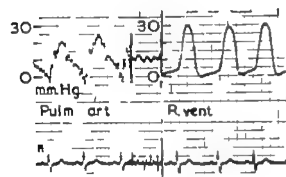


Fig. 3. M surements of pressure in pulmonary artery and right entricle obtained by catheterization of the right side of the heart.

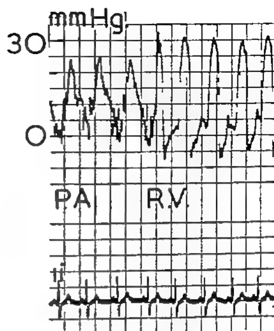


Fig. 4. Recording of pressure made during withdrawal of the catheter from the pulmonary artery to the right ventricle.

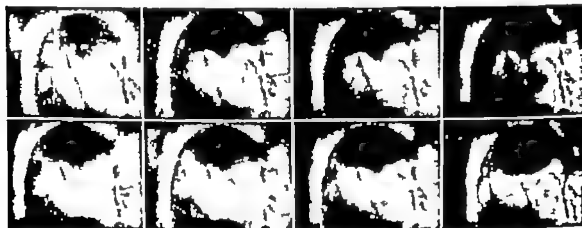


Fig. 5. A trip of the lateral cineangiocardiogram demonstrating reflux of contrast med um from the pulmonary artery (sit of i jection) int the dilated right entricle.

hanged. A mid-dia tolic murmur w recorded in the i flow tract of the entricle nd it w accentuated during inspiration. A loud trial sound also present (Fig. 7). When the catheter was removed t the right trum both systolic and di astolic murmurs disappeared.

Discussion

Our clinical diagnosis was based on the presence of a murmur known to have been present from an early age. A hyperdynamic right entricle with a systolic and diastolic murmur heard best in the pulmonary area associated with aneurysmal dilatation of the main pulmonary artery without any pulmonary plethora was in favor of primary pathology of the pulmonary valve.

Delayed dia tolic murmurs have been reported in aortic incompetence (Leatham)

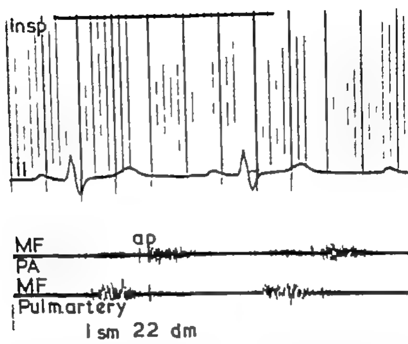


Fig 6 Phonocardiogram, with simultaneous recording from the pulmonary area and from the pulmonary artery. The ejection type of systolic murmur was best recorded from inside the pulmonary artery whereas the diastolic murmur was louder on the chest II.

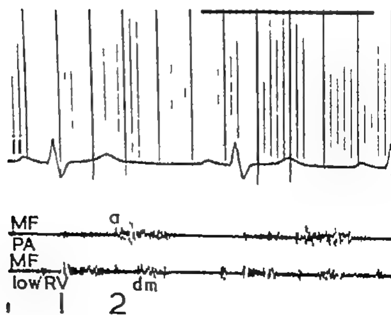


Fig 7 The phonocatheter recorded early systolic murmur and mid-diastolic murmur in the inflow tract of the right ventricle.

but this diagnosis was excluded on clinical grounds. There was a normal pulse pressure and the long loud medium frequency diastolic murmur and thrill were maximal in the pulmonary area. The murmur was unlike the more high-pitched early diastolic murmur of aortic incompetence. The presence of a normal ascending aorta on the radiograph and the right axis deviation and right ventricular hypertrophy on the electrocardiogram were both points against the diagnosis of an aortic lesion.

The presence of a mid-diastolic murmur accentuated by inspiration was of considerable interest. The murmur was best heard at the lower left sternal edge. Clinically, the comparison was made with the Austin Flint type of mid-diastolic murmur which is sometimes heard in aortic incompetence. The phonocatheter enabled us to confirm that the mid-diastolic murmur was heard and recorded with the tip of the catheter situated just beyond the tricuspid valve in the inflow tract of the right ventricle. It is suggested that the murmur was due to turbulence in the right ventricular inflow tract caused by considerable reflux of blood into the dilated right ventricle. Such a murmur has not been reported previously.

The presence of a similar end-diastolic pressure in the right ventricle and pulmonary artery has been used as a diagnostic point in pulmonary incompetence.[4,6] In addition, our patient had a small peak systolic gradient over the pulmonary valve. Such a gradient has been seen in experimental and acquired pulmonary incompetence.[4] It is thought to be due to the increased stroke volume of the right ventricle and analogous to the systolic gradient seen in some cases of atrial septal defects with large left-to-right shunts, but without organic pulmonary valve stenosis.

The diagnosis was confirmed in a striking manner using selective cineangiocardiography. The study shows such dilatation of the right ventricle as to make it unlikely that the lesion would be innocuous (Fig. 5). In experiments with dogs, pulmonary incompetence is tolerated much better than a similar degree of aortic incompetence.[4] It is self-evident that the diastolic overload would necessitate a great increase in the work done by the right ventricle in order to maintain a near-normal forward pulmonary blood flow.

The anatomy of the right ventricle is such that this chamber can eject a large volume of blood with minimal amounts of myocardial shortening.[9] Large volumes of blood can be pumped against a low resistance, but a sudden rise in pulmonary vascular resistance might lead to right ventricular failure because of the difficulty of sustaining high pressures in the right ventricle.

In general, the clinical consequences of pulmonary regurgitation are not serious in our experience; one patient lived to the age of 60 years, with little disability from the valvular lesion. One of the patients reported on by Ford and associates[4] died at the age of 44 years after progressive heart failure. Two of the 9 patients whose cases were discussed by Lendrum and Shaffer[11] were reported to have symptoms due to their pulmonary incompetence. Their own patient, a 16-year-old boy, had no symptoms and was leading a normal active life. Although our patient is presently free from symptoms, she may develop exertional dyspnea and right heart failure.

Summary

The case of a patient with isolated congenital pulmonary valve incompetence is described. The clinical diagnosis was confirmed by cardiac catheterization and cineangiocardiography. A phonocatheter made it possible to analyze the pulmonary systolic and diastolic murmurs which were localized to the pulmonary artery and right ventricle. A medium frequency mid-diastolic murmur was heard and localized to the inflow tract of the right ventricle. It is suggested that this murmur is similar to the Austin Flint type of diastolic murmur which is sometimes heard in cases of aortic regurgitation.

We wish to thank Dr Jane Howqua[illegible], who kindly referred the patient for investigation. Dr W. S. C. Hare was responsible for the cineangiocardiography.

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A large aneurysm of the mitral valve

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Aneurysms of the mitral valve although much less common than aneurysms of the aortic valve are well recognized complications of bacterial endocarditis and have recently been reviewed by MacLean and MacDonald Usually they affect the anterior or aortic cusp of the mitral valve and may project into either the left atrium or the left ventricle. If large in size they are saccular and have wide mouths with blood clot in the sac Soulié and Porge[4] believed that they arose in consequence of a spread of an endocarditis from the aortic valve onto the anterior cusp of the mitral valve However aneurysms sometimes arise on the posterior cusp and in the absence of bacterial endocarditis so that the foregoing explanation is not all inclusive Saphir and Leroy[2] suggested that in contradistinction to the false thromboaneurysms of Ribbert arising in bacterial endocarditis there are true aneurysms which develop through a portion of the valve cusp weakened by a valvulitis that gives way under the intraventricular pressure Renwick and Stewart recorded in a 63 year-old woman the rapid development of an aneurysm of the mitral valve in association with the development of iridocyclitis. No specific cause for the aneurysm could be found We have recently encountered a very large aneurysm of the mitral valve of uncertain causation in an adult African

Case report

The patient a male Kikuyu who was about 45 years old was hospitalized with a 3-month history of palpitations, effort dyspnea cough production of frothy sputum and swelling of the ankles. H had been gradually getting worse On direct inquiry he gave a history of penile chancre while in the army in 1943 This he said had been treated [illegible] examination he was febrile. His temperature was usually 99 0°F but peaks of 102°F occurred every 3 to 4 days. A faint scar was seen on the dorsum of the penis. H was somewhat anemic and had moderate clubbing of the fingers. His spleen was palpable 3 inches below the right costal margin and was a little tender His jugular venous pressure was elevated There was some bilateral ankle edema The pulse was regular and collapsing the rate was 120 per minute The apex beat was in the sixth intercostal space 4½ inches from the midline and was of left ventricular quality On some occasions systolic thrill was felt at the apex. On auscultation typical aortic diastolic murmur was heard maximal in the right second intercostal space close to the sternum. At the apex loud (Grade 4/6) pansystolic murmur was heard radiating to the axilla There were no added sounds and no mitral diastolic murmur was heard. The blood pressure was 140/40 mm Hg The fundi showed severe chorioidoretinitis.

A white blood cell count was 6,200 with 72 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophils. The hemoglobin was 62 per cent (9 1 Gm per cent) and the absolute values showed iron deficiency The erythrocyte sedimentation rate (Westergren) was 37 mm in 1 hour A heavy growth of pneumococci was recovered from the sputum Three blood cultures grown before any treatment was commenced were all negative No abnormalities were found in the urine It did not contain red blood cells. A blood Kahn reaction was positive A chest radiograph (Fig 1) and screening revealed that th

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left ventricle was moderately enlarged and that the left atrium was enlarged although not markedly so. There was no evidence of enlargement of the right side of the heart. Several electrocardiograms were recorded and the findings varied little. They showed left axis deviation with deep S waves (20 mm.) in Lead V₁, suggestive of left ventricular enlargement, and inverted T waves over the right precordium as far as Lead V suggestive of right ventricular hypertrophy or the Bantu variant of the normal which is seen quite commonly in the Kikuyu. The P waves were broad and plateau-topped in all the records: the maximum duration was 0.12 second and the maximum height was 3 mm. in Lead II which is suggestive of left atrial enlargement. There was also marked digitalis effect.

Diagnosis was difficult. It was decided that the patient had syphilitic aortic incompetence and that it was complicated by subacute bacterial endocarditis, although this was never proved. A palpable spleen in a patient in this part of the world is of no use as evidence, so that this diagnosis rested only on the pyrexia and clubbing in association with a known heart lesion. The cause of the mitral incompetence, in spite of much discussion, remained uncertain.

The patient was digitalized and given thiazide diuretics. He was also given two mega-units of crystalline penicillin daily for 6 weeks. His temperature had, in fact, settled before the penicillin was started and never rose again. His heart failure responded moderately well.

At this stage the patient insisted on his discharge, but had to be readmitted 1 week later. He was again in congestive cardiac failure. There were no changes in the physical signs nor in the chest radiograph. The electrocardiogram showed that the right precordial T-wave inversion had disappeared, and that the digitalis effects were much more marked. In spite of some response to injections of mersalyl, he collapsed and died after 2 weeks in the hospital.

Autopsy findings. There was evidence of severe congestive cardiac failure in the liver, kidney, spleen, and lungs, but no infarcts, old or recent, were found. The heart was much enlarged; it weighed 600 grams and showed marked left ventricular dilatation and hypertrophy (2.5 cm.). The right atrium, tricuspid valve (120 mm.), and the right ventricle showed no lesions, other than a slight degree of dilatation and hypertrophy of the ventricle (7 mm. in the outflow tract). The pulmonary valve was normal (90 mm.), and the artery showed no lesions. The left atrium was dilated. The cause of the left ventricular hypertrophy lay in the aortic valve and aorta; the latter was dilated and showed severe syphilitic and atheromatous changes. The valve cusps were similarly affected; the commissures were widened and the cusp edges thickened, rolled, and retracted. All three cusps were present. There was no evidence of calcification or of bacterial infection. The coronary orifices were patent and the coronary arteries were normal.

The aortic surface of the anterior cusp of the mitral valve was smooth and showed no evidence of infection. High up, at the base of the cusp was an oval hole about 1 cm. in its greatest diameter with uniformly smooth edges. The opening led into



Fig. 1. The chest radiograph taken 7 weeks before death shows an enlarged left ventricle, dilated unfolded aorta, and atrial enlargement.

large aneurysm of the mitral valve which hung down through the valve orifice as a collapsed bag of firm gray-brown tissue over the surface of the anterior cusp, descending about 0.7 cm. below the free margin so that it was about 3.2 cm. in length from base to tip (see Figs. 2 and 3). When the tip of the sac was raised, the underlying valve edges were found to be normal, and the free edge measured 120 mm.

The base of the sac was high up on the mitral valve cusp and arose over an area 1.7 cm. wide. On this, the side of the orifice, there were four openings into the sac. The largest was about 1.4 cm. long and 0.8 cm. wide, roughly oval in shape and anterior to the postero-upper end of the aneurysm. It was exactly opposite the opening from the aortic side, so that one could look directly through the aneurysm at this point. A lunate opening of smaller size was present at the same level slightly anterior to the largest opening. The third opening was about halfway down the sac and, again, was irregularly oval in shape. At the tip and in the collapsed part of the aneurysm opening toward the aortic side was the fourth one, an oval orifice about 1 cm. in its greatest diameter. Measurements were difficult to make because of the collapsed state of the aneurysm. Noteworthy was the fact that all these openings had smooth rolled edges without evidence of infection or recent tearing. (The orifices are best seen in the artist's sketches in Fig. 4.)

The outside walls of the sac were smooth and folded and showed no evidence of infection. The tissue was quite pliable and tough. Inspection of the inside showed smooth brown-gray surfaces, with no large thrombi but with tiny clots in some of the interstices. There was no calcification or infection and everything pointed to this being a long-standing lesion—a smooth-walled bag with multiple openings.



Fig. 2. H rt showing aort surfac of mitral h w h probe unfice lead ng neurysm.

The whole p w h the neurysm was removed and he neurys m packed and block sections were made

The wall of he sac w omposed of fibrou tissue wh h m ined few hin-walled essels nd oc sional mall are of fibrinoid necrosis It was de ed of nflammat ry cell filtr ions All the aces nd the whole of he erior of the sac were l ned b endothelial Th There were never l small old thrombi he sac partially org nized and overed b endotheli m The h tself w normal nd he endothelium w otherwise smal fec ed The endothelium of he out ide of the sac howed he adherence of few fibri tags, nd some area hese tags had been org nized and in corpor ed in fibrou issue One of he larger of these h wed few gr m d als fied ma erial The lack of cell ltr tion w trik ng feature of the l and aneurys mal sac nd one ould see no evidence of old or recen bacterial endo rdit s The aortic l es nd aort howed evidence of yphil ic dise se nd atheroma but no ev dence of bacterial endocard is The myocardi m showed no evidence of old rheuma lesions nd he l es of the right ide of the heart were normal The use of the aneury m ould not be ertained

Discussion

The pathogenesis of thi very large aneurysm of the mitral valve is obscure The dominant feature was aortic syphilitic disease which severely affected the aortic valve and caused aortic incompetence Blood cultures in the early stages were negative and terminally no infarcts were found The patient was pyrexial in the early stages but the pyrexia subsided before penicillin treatment had begun. The heart failure was never fully controlled It might be that there was a very early mitral bacterial endocarditis which was cured by the antibiotic before marked lesions had developed It seems unlikely that there was any aortic endocarditis.

Evidence of a valvulitis was also lacking save that there was a slight degree of vascularization of the mitral leaflet. The flow in the aneurysm was presumably from ventricle to atrium with the blood entering the subaortic round hole and emerging via the numerous openings on the atrial side The size of the aneurysm was such that it had partially obstructed the atrioventricular communication Presumably in systole the aneurysm ballooned into the left atrium and blood passed through from the ventricle to the atrium producing the mitral systolic murmur and thrill It will be recalled that the openings were so placed that direct and easy communication was possible from the ventricle to the atrium via the aneurysm. In diastole the aneurysm probably sagged and partially occluded the mitral orifice although no mitral diastolic murmur was ever heard These two effects would explain the left atrial enlargement A rise in left atrial pressure behind the ob-



Fig. 3. Mitral aneurysm as seen from the atrial side of the anterior mitral cusp showing multiple openings.



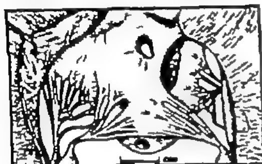


Fig. 4. Artist sketches of the aneurysm from the atrial aspect (*top*) and from the aortic aspect (*bottom*).

structed mitral orifice could explain the hypertrophy of the right ventricular out flow tract and the inverted T waves over the right precordium in the earlier elec trocardiograms. In the case reported by Musallam and McCall[2] the physical signs and electrocardiogram resembled those of mitral stenosis.

Clinical diagnosis was difficult. The obvious diagnosis would have been rheumatic heart disease with incompetence of the aortic and mitral valves. However the good history of syphilis and the positive Kahn reaction suggested a syphilitic etiology and the absence of a third heart sound and mid-diastolic mitral murmur was unlike rheumatic mitral incompetence. Other possibilities were in addition to the syphilitic aortic incompetence, there was endomyocardial fibrosis of the left ventricle with mitral valve incompetence or there was functional mitral incompetence although this is uncommon or a valve cusp had perforated from the subacute bacterial endocarditis which we had supposed to exist. It is not surprising that the correct explanation of the mitral murmur was never even considered

Summary

A clinical and pathologic account is given of the case of an African patient with syphilitic aortic incompetence who also had a loud mitral systolic murmur This murmur proved to be due to a large aneurysm of the anterior cusp of the mitral valve through the openings of which blood could pass from the left ventricle to the left atrium Most of the cases reported have been due to bacterial endocarditis. The etiology of the case described here is uncertain There was no postmortem evidence of bacterial endocarditis.

We wish to thank Mr R. T unliffe, F.I.M.L.T for the photographs and preparations, nd M P Call M.I.M.A., for the sketches

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Fig. 2. Heart showing aortic surface of mitral valve with probe in situ leading to aneurysm.

The whole cusp with the aneurysm was removed and the aneurysm packed and block sections were made.

The wall of the sac was composed of fibrous tissue which contained a few thick-walled vessels and occasional small areas of fibrinoid necrosis. It was devoid of inflammatory cell infiltrations. All the surfaces and the whole of the interior of the sac were lined by endothelial cells. There were several small, old thrombi in the sac partially organized and covered with endothelium. The cusp itself was normal and the endothelium was otherwise unaffected. The endothelium of the outside of the sac showed the adherence of a few fibrin tags, and in some areas these tags had been organized and incorporated in fibrous tissue. One of the larger of these showed a few grains of calcified material. The lack of cell infiltration was a striking feature of the walls of the aneurysmal sac and one could see no evidence of old or recent bacterial endocarditis. The aortic valves and aorta showed evidence of syphilitic disease and atheroma but no evidence of bacterial endocarditis. The myocardium showed no evidence of old rheumatic lesions and the valves of the right side of the heart were normal. The cause of the aneurysm could not be ascertained.

Discussion

The pathogenesis of this very large aneurysm of the mitral valve is obscure. The dominant feature was aortic syphilitic disease which severely affected the aortic valve and caused aortic incompetence. Blood cultures in the early stages were negative and terminally no infarcts were found. The patient was pyrexial in the early stages but the pyrexia subsided before penicillin treatment had begun. The heart failure was never fully controlled. It might be that there was a very early mitral bacterial endocarditis which was cured by the antibiotic before marked lesions had developed. It seems unlikely that there was any aortic endocarditis.

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Fig. 3. Mitral aneurysm seen from the atrial side of the anterior mitral cusp, showing multiple openings.

newborn infants. When murmurs are present they are usually of the systolic ejection type. Such a murmur frequently indicates valvular stenosis, patent ductus arteriosus or occasionally a ventricular septal defect Differentiating between these anomalies by employing auscultation alone may be impossible. Diastolic murmurs in the newborn period are exceedingly rare

By itself the history of one episode of pneumonia at the age of 4 years is not unusual. When taken with the knowledge that the patient had a cardiac murmur one might suspect a left to-right shunt

The physical findings would indicate moderate pulmonary hypertension This opinion is based upon the fact that the second component of the second sound at the left cardiac base (pulmonary closure) was equal in intensity to the first component of the second sound in this area (aortic closure) The absence of an ejection click and the equal intensity of both components of the second sound would be evidence against either significant pulmonary valvular obstruction or severe pulmonary hypertension. Furthermore a lift of the right ventricular type was present. It would be helpful to know whether the activity of the right ventricle was increased over that of the normal.

DR. ELLIOTT The right ventricular activity as determined by precordial palpation was considered to be hyperdynamic.

DR. ELIOT The hyperdynamic right ventricle would make one consider strongly a left to-right shunt since the right ventricle appears to have been handling an increased stroke volume In the case of obstruction to right ventricular outflow or in pulmonary hypertension the action of the right ventricle is different from that described by Dr Elliott.

In pulmonary valvular stenosis right ventricular infundibular stenosis or pulmonary hypertension palpation at the left sternal border often reveals a slow and forceful elevation of the precordium

The systolic murmur described seems to be characteristic of a ventricular septal defect a condition which I believe, is justifiably diagnosed at this point The basis for the diastolic rumble at the apex is not entirely clear Its timing and location suggest a flow murmur related to a ventricular septal defect. It is unlikely that a flow murmur located at the cardiac apex would result from a left to-right shunt at the atrial level associated with increased flow across the tricuspid valve

The normal systemic diastolic pressure described in this case does not favor a diagnosis of patent ductus arteriosus with



Fig 1 Thoracic roentgenograms *Left* Frontal view *Right* Lateral view demonstrating minimal posterior displacement of the barium-filled esophagus.

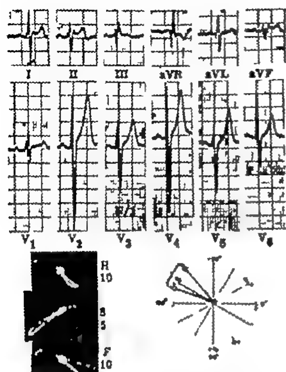


Fig 2 Electrocardiogram vectorcardiogram and hexaxial reference system. In the *scalar electrocardiogram* (V/2 = 1/2 standardization) normal sinus rhythm is present and the major QRS axis is indeterminate but probably lies between +210 and +240 degrees in the frontal plane The QRS, P R, and Q-T interval are normal. The RSR'S' complex recorded in Lead V result from the figure-of-eight loop in the horizontal plane Right ventricular hypertrophy is suggested by the delayed intrinsicoid deflection (0 06 sec), in the right-sided precordial leads, and by the deep S waves in Lead V Left ventricular hypertrophy is indicated by the magnitude of the combined voltage of the R and S component of the QRS complex in Lead V (90 mm), as well as the S' wave in Lead V The major T vector is increased in amplitude indicated by peaked T waves in Precordial Leads V through V The *vectorcardiogram* demonstrates "figure-of-eight" loop in all planes of the type suggesting biventricular hypertrophy Furthermore the terminal forces move anteriorly and to the right as is found in right bundle branch block. In summary the electrocardiogram demonstrates biventricular hypertrophy and suggests a probable right bundle branch block.

left-to-right shunt In that condition the diastolic pressure is often but not universally low The roentgenograms do not add materially to the clinical data (Fig 1)

Let us review the electrocardiograms and vectorcardiogram (Fig 2) The scalar electrocardiogram reveals sinus rhythm The major QRS axis is indeterminate but probably lies between +210 and +240 degrees in the frontal plane The QRS P R and Q-T intervals are normal The RSR'S complex recorded in Lead V_1 results from the figure-of-eight loop in the horizontal plane There are deep S waves in Lead V_6. Right ventricular hypertrophy is suggested by the delayed intrinsicoid deflection (0 06 seconds) in the right precordial leads, and by deep S waves in Lead V_6. Left ventricular hypertrophy is indicated by the magnitude of the combined voltage of the R and S components of the QRS complex in Lead V (90 mm) as well as by the presence of the S wave in Lead V_1 The major T vector is increased in amplitude as indicated by peaked T waves in Precordial Leads V_2 through V_6.

The vectorcardiogram demonstrates a figure-of-eight loop of the type which suggests biventricular hypertrophy in all planes. Furthermore the terminal forces move anteriorly and to the right suggesting right bundle branch block. In summary the electrocardiogram demonstrates right bundle branch block and biventricular hypertrophy With the exception of the electrical axis the vectorcardiogram is similar to that found in anomalies of the persistent common atrioventricular canal type.

Dr Wang would you discuss the observations during cardiac catheterization

DR WANG Before cardiac catheterization was performed all clinical data were considered Our reasoning was in concert with what Dr Eliot has said in that a ventricular septal defect with moderate pulmonary hypertension was believed to be present As we began our study however definite and marked arterialization was found to be present at the atrial level (Table I) In view of this finding the appearance-time of inhaled methyl iodide[131] was measured in the left pulmonary artery and in the lower portion of the right atrium (Fig 3) In these location early appearance of methyl iodide was confirmed when a comparison was made with simultaneous determination obtained in the right radial artery The presence of a left-to-right shunt at or proximal to the atrial level was indicated

The possibility that a partial anomalous

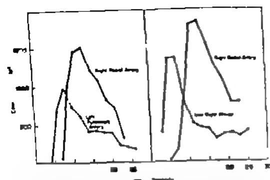


Fig. 3. Methyl iodide[131] inhalation studies. The time of the appearance and the activity of inhaled material at the radial artery is normal. The early appearance at the left pulmonary artery and at the lower portion of the right atrium is indicative of left-to-right shunt into the right atrium or proximal to it.

pulmonary venous connection existed was then explored to a limited degree. The oxygen saturation of samples from the superior vena cava was high (92 per cent). Within the superior vena cava it was possible, however, to move the tip of the catheter proximal to the level of arterialization. The catheter was then moved to the right subclavian vein where the oxygen saturation was found to be 78 per cent; the reading in the inferior vena cava was 80 per cent. The catheter did not enter the left innominate vein. From these findings, anomalous pulmonary venous connection to the superior vena cava could not be excluded. Therefore, dye-dilution curves were determined by injecting Cardiogreen successively into each pulmonary artery and into the superior vena cava while taking samples from the right radial artery (Fig. 4). The appearance time of dye from each injection was normal, thereby ruling out a central right-to-left shunt. In each there was distortion and prolongation of the disappearance-slope and, in the absence of cardiac failure or left-sided valvular insufficiency, these curves indicated a left-to-right shunt.

Of primary importance was the disparity in the degree of distortion of curves obtained by injecting into the left and the right pulmonary arteries. The greater distortion of the curve obtained by injecting into the left pulmonary artery indicated a greater contribution of the pulmonary vascular bed on the left side to the left-to-right shunt. The greater pulmonary flow on the left side is opposite to that usually found in atrial septal defect of the fossa ovalis type.[3]

Second, the curve obtained by injecting into the right pulmonary artery demonstrated a normal build-up, whereas that obtained by injecting into the left pulmonary artery demonstrated a distinct break in the build-up. This break in the curve obtained by injection into the left

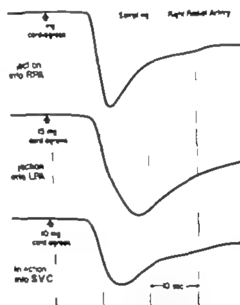


Fig. 4. Dye-dilution studies performed by injecting Cardiogreen into the lesser circulation. All curves were obtained from the right radial artery. The appearance-time in all curves is normal, ruling out significant right-to-left shunt from a cardiac chamber or pulmonary artery. Each curve demonstrates distortion of the disappearance-slope. In the absence of left-sided valvular insufficiency or cardiac failure this indicates a left-to-right shunt. *Upper curve:* After injection into the right pulmonary artery (*RPA*) there is a slow return to the base line. When compared to the *center curve* which represents injection into the left pulmonary artery (*LPA*), there is a much greater distortion of the LPA than the RPA curve. This would indicate a greater contribution of the left than the right pulmonary vascular bed to the total left-to-right shunt. The distortion of the disappearance-slopes of both the right and left pulmonary arterial curves reflect the left-to-right shunt. The early distortion of the curve from the left pulmonary artery indicates flow through an anomalous pulmonary venous connection or connections. *Lower curve:* Injection into the superior vena cava (*SVC*) results in a composite pattern of both the left and the right pulmonary arterial injections.

Table I Summary of cardiac catheterization data

Sampling site	*Pressure (mm Hg)*	*Oxygen saturation (per cent by oximetry)*
Right subclavian vein	—	78
Superior vena cava (high)	—	92
Inferior vena cava (at diaphragm)	—	80
Right atrium (superior and lateral)	—	88
Right atrium (central and lateral)	6/4	84
Right atrium (inferior and lateral)	—	[illegible]
Right ventricle (superior)	50/0-8	88
Right ventricle (inferior)	65/0-9	83
Pulmonary trunk	30/10	85
Right pulmonary artery	20/5 (Mean, 15)	88
Left pulmonary artery	30/10	87
Right radial artery	120/60 (Mean, 80)	98

*Oxygen content = [illegible] vol per cent in the right pulmonary artery and 20.9 vol per cent in the right radial artery
Oxygen capacity = 20 vol per cent oxygen consumption = 240 [illegible]/min
Pulmonary arterial wedge pressures = 11 mm. Hg = 9 mm. Hg = 12 mm. Hg; mean = 11 mm Hg.
Systemic flow = 5 L./min index = [illegible] L./min./M
Pulmonary flow = 10.3 L./min index = 7.0 L./min./M
Resistance Systemic = 990 dynes sec cm total pulmonary = 124 dynes sec cm pulmonary arteriolar = 40 dynes sec cm

pulmonary artery corresponds in time to the peak concentration of the curve obtained by injection into the right pulmonary artery and therefore is not due to a right-to-left shunt but is rather the peak of the primary curve This indicates that a lesser portion of the injected dye is traversing the normal pathway Most of it is recirculated through the lungs as indicated by the larger peak following This is characteristic of curves in anomalous pulmonary venous drainage

The curve obtained by injecting into the superior vena cava was a composite of that from the right and left pulmonary arterial injections and showed no early break to indicate a right-to-left shunt

Review of the data at this point favored a left-to-right shunt at or proximal to the atrial level The dye curve from the left pulmonary artery indicated anomalous pulmonary venous connection from the pulmonary vascular bed on the left side The precise anatomic location of the connection was not defined however

From oxygen saturation data alone we were unable to confirm the clinically suspected additional shunt at the ventricular level Therefore selective left ventriculography was performed The catheter was introduced into the left ventricle in a retrograde fashion from the aorta (Fig 5) Forty cubic centimeters of 90 per cent Hypaque was injected into the left ventricle Biplanar angiocardiograms gave evidence of a small defect in the basal aspect of the ventricular septum No other abnormality was detected

One peculiar finding was evident in the data of the cardiac catheterization (Table I) The mid right atrial pressure was found to be 6/4 mm Hg whereas the mean pulmonary arterial wedge pressure was found to be 11 mm Hg When an atrial septal defect is present both atrial pressures are equal and the pulmonary arterial wedge pressure would be expected to be equal to the right atrial pressure The disparity present in this case was puzzling and suggested the possibility that the atrial septum was intact and that the left-to-right shunt was a result of partial anomalous pulmonary venous connection.

In summary it was our diagnosis that there was a moderate left-to-right shunt at the atrial level or proximal to it The exact site of the shunt was not certain but the possibility of partial anomalous pulmonary venous connection from the left lung was considered The presence of a ventricular

septal defect was confirmed by selective left ventriculography but the defect appeared to be a small one. The slight systolic pressure gradient between the right ventricle and the pulmonary artery was considered to be a result of the large flow across the pulmonary valve a manifestation of the large left-to-right shunt.

DR. ELLIOTT Thank you Dr Wang Dr Varco would you tell us of your operative findings and the postoperative course in this patient.

DR. VARCO After extracorporeal circulation had been established the right atrium was opened A small probe-patent foramen ovale was closed first Then the right ventricle was opened and a basal ventricular septal defect was closed. No disturbance in conduction developed A left superior vena cava was believed to exist No other abnormalities were detected during the operation. The patient tolerated the procedure well

On the third postoperative day the patient developed slight fever and rapid refractory tachycardia. The blood pressure and urinary output remained normal On the sixth postoperative day cardiac arrest occurred Closed-chest cardiac massage and drugs were unsuccessful in reestablishing cardiac action

DR. ELLIOTT Thank you Dr Varco Dr Edwards, would you please discuss the findings at necropsy

DR. EDWARDS At necropsy no specific cause of death could be identified although interesting anatomic details of the thoracic veins were observed (Figs. 6 and 7) The heart was enlarged it weighed 460 grams. The great arteries were normally related The right and left ventricles were hypertrophied they measured 1 2 and 1 8 cm in thickness respectively

The right upper and lower and the left lower pulmonary veins joined the left atrium in a normal fashion. The left upper pulmonary vein joined the left innominate vein rather than the left atrium. An anomalous vein-like vessel extended from the expected location of the ostium of the left upper pulmonary vein in the upper part of the left atrium on one hand to the coronary sinus, on the other The anomalous vein passed downward along the anterior wall of the left atrium and after running anteriorly to the left lower pulmonary vein it turned posteriorly to join the coronary sinus. An atretic strand extended from the left upper pulmonary vein and the proximal part of the anomalous vein which ran between the left atrium and the coronary sinus. The coronary sinus was in the normal position but was very slightly increased in diameter Its right atrial ostium was narrow and measured only 5 mm in diameter The degree of narrowing



Fig 5 Selective left ventriculogram the catheter was introduced in retrograde fashion through the aortic valve. *Left*. Frontal view *Right*. Lateral view Forty cubic centimeters of 90 per cent Hypaque was injected The arrow in each view points to a stream of opaque material passing through the small ventricular septal defect.

primitive connection to the left innominate vein and ultimately to the right anterior cardinal vein

Use of this primitive channel appears to have been the basis for its retention From the viewpoint of pathology this channel is termed an *anomalous connection* of the left upper pulmonary vein to the left innominate vein

In the left atrium the ostium of the anomalous venous channel is to be considered the true ostium of the left upper pulmonary vein The channel leading from this ostium to the coronary sinus is to be viewed as having two contributions. Near the left atrium the channel represents the left upper pulmonary vein. More distally (toward the coronary sinus) the channel is to be considered as a persistence of a *primitive connection between the left* upper pulmonary vein and the left anterior cardinal vein The coronary sinus itself is the proximal segment of the left anterior cardinal vein

The connection between the left atrium and the coronary sinus may be termed a *levoatriocardinal* vein This term was proposed for an anomalous vein which runs between the left atrium and any derivative of the cardinal venous system. Primarily such channels represent anomalous connection of a pulmonary venous segment and a cardinal venous derivative after which the pulmonary venous segment is normally incorporated into the left atrial wall.

Usually when a levoatriocardinal vein is present there is mitral atresia with a narrow or closed foramen ovale[8] Persistence of a primitive venous connection in such cases, is explained by obstruction to the flow of blood in the normal direction while early connections between the pulmonary and systemic veins are still present. Such connections serve as collateral pathways for the flow of pulmonary venous blood

In the current case the levoatriocardinal

(Fig 8 For legend see opposite column)

Fig 8 *The upper panel* shows the normal junction of the individual pulmonary veins (*R.L.*, *R.U* *L.L.*, *L.U*) with a protrusion known as the common pulmonary vein (*C.P.V.*) from the sinoatrial region (*S.A.*) of the heart In addition, the left upper pulmonary vein (*L.U*) has maintained primitive connection with two veins, (1) the left anterior cardinal vein (*L.A.C.*) and (2) the right anterior cardinal vein (*R.A.C.*), through the vein that is to become the left innominate vein. *R.S.* and *L.S* Right and left subclavian veins, respectively *R.J* and *L.J* Right and left internal jugular veins, respectively *The center panel* illustrates the beginning of narrowing within the left upper pulmonary vein (*L.U*) near the left atrium (*L.A.*). The connections of the left upper pulmonary vein with the cardinal veins are retained. *The lower panel* shows the stage found at necropsy The intermediate segment of the left upper pulmonary vein (*L.U*) is now atretic The venous drainage of the left upper pulmonary lobe is into the left innominate vein, as a result of retention of the primitive *connection with the right anterior* cardinal vein At the atrial aspect, the left upper pulmonary vein (*L.U*) has become incorporated into the left atrial wall (*L.A.*) while retaining its connection with the left anterior cardinal vein. The latter has gone through the normal stages of change resulting in its proximal portion becoming the coronary sinus. Stenosis of the right atrial ostium of the coronary sinus may have been the *stimulus for retention of* the primitive connection between the left anterior cardinal vein and the left upper pulmonary vein. The right anterior cardinal vein has become the superior vena cava (*S.V.C.*).

vein might have served as a collateral channel for coronary venous blood It will be recalled that the right atrial ostium of the coronary sinus was narrow This state may have been present early In the face of obstruction at the right atrial aspect of the coronary sinus, a primitive connection (now representing the anomalous channel between the left atrium and the coronary sinus) might have carried coronary venous blood into the left upper pulmonary vein With further changes as outlined the ultimate result was connection of the coronary sinus with the left atrium. It is possible therefore that a small right to-left shunt into the left atrium occurred through this route.

DR. ELLIOTT Dr Eliot would you comment in retrospect on the physiologic aspects of this case.

DR. ELIOT The oxygen saturation in the superior vena cava was higher than that in the inferior vena cava, the opposite of that normally found. Either of two situations may account for this. One is reflux of blood into the superior vena cava in the presence of an atrial septal defect and the second is anomalous pulmonary venous connection to the superior vena cava. Had it been possible to pass the catheter into the left innominate vein the anomalous pulmonary venous connection which was present would have become evident.

The disparity between the pulmonary arterial wedge" pressure and the right atrial pressure was consistent with a functionally intact atrial septum Recognition of the significance of this finding can be used to exclude an atrial septal defect as the basis for the left to-right shunt at the atrial level.

Left and right pulmonary arterial dye dilution curves indicated that the greater contribution to the left to-right shunt came from the left lung This favors anomalous pulmonary venous connection from the left lung rather than an atrial septal defect. The pattern of the downslope in the curve obtained by injecting into the left pulmonary artery was characteristic of anomalous connection of a left pulmonary vein

Diagnosis . Partial anomalous pulmonary venous connection ventricular septal defect and anomalous communication of left atrium with coronary sinus

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Fundamentals of clinical cardiology

Use of the electrocardiogram in exercise tests

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The large literature accumulated in the twenties and thirties, on exercise tests using hemodynamic and metabolic functions in heart disease was reviewed 20 years ago.[1] Since the early thirties, the electrocardiographic exercise test has increasingly replaced these testing procedures following Feil and Siegel's observation[2] of similar electrocardiographic changes in spontaneous attacks of angina pectoris and in attacks induced by exercise. Goldhammer and Scherf[3] were the first to suggest the use of the electrocardiographic changes after moderate exercise as a means of early diagnosis of latent coronary insufficiency. The abnormal ECG response to exercise is most frequently due to localized ischemia, whereas other testing procedures reveal general circulatory, respiratory, and metabolic reactions to exercise and their disturbance in latent cardiac or pulmonary insufficiency. Therefore, a different (and additive) type of information is obtained by using changes in the ECG and in other circulatory and metabolic functions as a criterion. According to a survey in 1960, the electrocardiographic exercise test was used in 70 per cent of 166 hospitals in 5 Midwestern states, which is probably fairly representative for North America.[4] This far exceeds the application of other special electrocardiographic procedures (ancillary leads, spatial vectorcardiogram, or other stress situations). The wide use of the electrocardiographic exercise test may be explained by the high prevalence of coronary artery disease in American and European populations and by the convenience of application of the test.

During the past two decades, an extensive literature on the electrocardiographic exercise test has accumulated, and the subject has been reviewed by Scherf and Schaffer,[5a] Lepeschkin,[6] Hellerstein, Prozan and associates,[7] and in Chapter 13 of my monograph. Some of the recent original communications also include an appreciable number of references. Rather than present another comprehensive review, I will concentrate on issues which are still controversial or on which attention has been focused recently. Since all criteria refer to conventional leads, vectorial changes will not be considered.

I. Standardization

The general design of the exercise test for diagnostic application is to effect an increase in myocardial oxygen demand to such an extent that it can be met by the increased coronary blood flow in the majority of healthy persons but not in the majority of patients with latent coronary insufficiency. (In patients with distinct coronary insufficiency by ECG or by

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history the exercise test for diagnostic purposes is contraindicated.) The best definition of the cardiac load during exercise is the cardiac oxygen consumption in cubic centimeters per minute per gram of heart weight. This is obviously impossible to obtain in routine situations. However, the total oxygen consumption in cubic centimeters per minute per kilogram of body weight in submaximal exercise must provide a good approximation. This follows from the high correlations between body weight and heart weight[illegible] and the linear relationship between oxygen consumption and cardiac output in submaximal work levels.[illegible] However, the correlation between total oxygen consumption and the minute volume is not perfect; the cardiac oxygen consumption increases more with the increase in heart rate than with the increase in stroke volume (in many patients with latent coronary insufficiency there is an excessive increase in the heart rate); the cardiac work increases with the elevation of arterial or intraventricular blood pressure and is, therefore, greater in patients with arterial or pulmonary hypertension. Cardiac work will also be greater for a given oxygen intake in the sedentary unconditioned individual than in the physically active individual because of the tendency for the blood pressure and heart rate to rise higher in the unconditioned man. Accordingly, even at the same total oxygen consumption the cardiac oxygen demand is greater in many patients than in healthy subjects, and perfect standardization of the exercise test is not possible. However, determination of total oxygen consumption is the closest approximation of cardiac load that we can obtain without heart catheterization.

It is surprising that more basic information with simultaneous determination of oxygen consumption and ECG during and after graded exercise is not available in spite of the large literature. We have measured oxygen consumption, pulmonary ventilation, and the ECG in 30 healthy (mostly older) subjects during and after walking on the treadmill at a speed of 3 miles per hour at grades of 0, 5, and 10 per cent.[9] The duration of the exercise was 15 minutes so that a steady state was obtained. The 12 lead ECG was taken before and after exercise with the subjects in the supine position, and a bipolar (frontal-dorsal) lead was taken while they were in the standing position before exercise and during walking. In 29 subjects there were no significant changes in the ECG, except in heart rate, with increasing severity of exercise. The heaviest load (10 per cent grade) with an average oxygen consumption of about 25 c.c. per minute per kilogram of body weight is close to the limit of aerobic work. Figs. 1 and 2 show representative examples. Fig. 3 shows the exceptional response of one subject with junctional S-T depression. Thus, the ECG response is not suitable for standardization of the exercise test. The lack of sensitivity of the ECG response to increasing work load raises the question whether the necessity of rigid standardization may have been exaggerated. However, standardization is necessary because there are distinct changes in the ECG of healthy people in severe anaerobic work (the differentiation between anaerobic and aerobic work level is extremely variable between individuals) and because a critical load level is needed to produce significant ECG changes in patients. This critical level can be attained in different types of work or in the same type of work by increasing the load or duration, or both. In the Master double-step test, as compared to the single test, both cardiac load and duration are increased; in the single Master two-step test of 1.5 minute duration the steady state is not yet attained so that the oxygen intake continues to rise for the 3 minutes of the Master double-step test. Thus, there is no superiority of one type of exercise over other types for diagnostic clinical application. In view of the lack of sensitivity of the ECG response to work loads and oxygen consumption over a large range (including the levels of the Master tests and other types of clinically used exercise tests), standardization has to follow the accepted principles of testing for physical fitness, i.e., work load rate and duration should be rigidly controlled, with correction factors for constitutional variables (age, sex, body weight, etc.). It should be realized that standardization of work load is only an approximation to standard

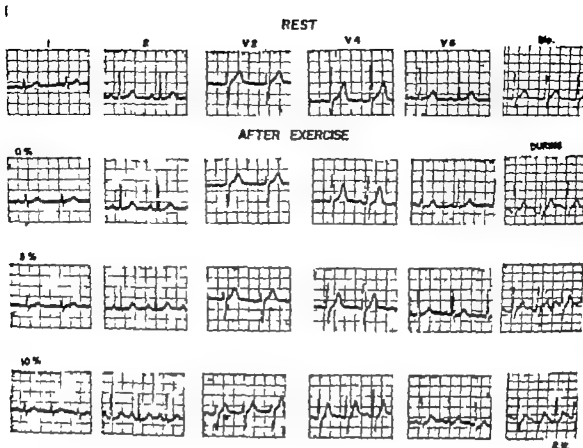


Fig. 1. Electrocardiograph Leads I, II, V, V (of R. W., healthy 43-year-old man with body weight of 72.4 kilograms) taken in the supine position at rest and after exercise (walking on the treadmill at speed of 3 m.p.h. at 0, 5, and 10 per cent grades for 15 minutes), and bipolar frontal-dorsal chest lead taken in the standing position and during walking (eighth to tenth minutes). The oxygen consumption per minute per kilogram was 13.4, 17.4, and 24.7 at 0, 5, and 10 per cent grades, respectively. The changes in the ECG are minor; the slight junctional S-T depression in Lead II at 10 per cent grade is due to atrial T wave.

ization of oxygen consumption, and even less so to the cardiac work load.

Master and Oppenheimer[4] attempted to provide a physiologically equivalent load for all individuals, taking into account age, sex, and particularly the body weight, since the heavier the patient, the more foot pounds of energy are consumed in walking the steps. Therefore, the work (number of ascents) is different for different individuals; a smaller number of ascents is required for a heavy than for a light subject. Objections against this type of standardization have been raised.[4] It also does not agree with military experience, as could be concluded from Zuntz and Schumburg's extensive investigation 60 years ago of oxygen consumption in prolonged walking.[22] Although the work in locomotion increases with the body weight, muscle mass and heart size are increased in proportion, so that there is an automatic adjustment.

Ford and Hellerstein[10] measured the oxygen consumption during and after the Master two-step test in 126 control subjects and 71 cardiac patients. One criterion for the validity of standardization is the interindividual variation; this was very large in Ford and Hellerstein's study—the 95 per cent normal limits of excess oxygen consumption (work plus recovery) ranged from about 1 to 2 liters (calculated from the standard deviation). The question whether this range of variability could be reduced by reference to body weight was not studied, so that Ford and Hellerstein's results do not give pertinent information

about the equality of the physiologic load in Master's standardization for different individuals.

Rowell and associates[14] compared the total oxygen consumption, oxygen per minute per kilogram of body weight, and per 1 square meter of body surface in Master's graded two-step test (using Master's procedure and tables) and in a step test with a constant number of ascents for all subjects. The 12 subjects investigated were grossly different in body weight so that the number of ascents in Master's procedure varied between 18 and 29. The standard deviation (S.D.) for oxygen consumption per kilogram was ±11.96 with Master's procedure and only ±4.87 when a constant number of steps was used (the results in terms of oxygen per square meter of surface were similar). Master's standardization penalizes the lightweight subject, who works much closer to his maximum oxygen intake (i.e., his maximum capacity) than does the heavier subject. Thus with Master's standardization tables an element of variation is added rather than eliminated. A constant number of ascents, e.g., 40 in 3 minutes, will provide a more uniform load than a varying number of ascents for different individuals. A single-step should be as suitable as a two-step test, with a correspondingly faster rate of ascents.

*In view of the high correlation between heart size and body weight, cardiac output and oxygen consumption, and the absence of correlation between mean arterial blood pressure and most of the range of body weight, cardiac work is related primarily to body mass, and the data must be standardized per kilogram of body weight.



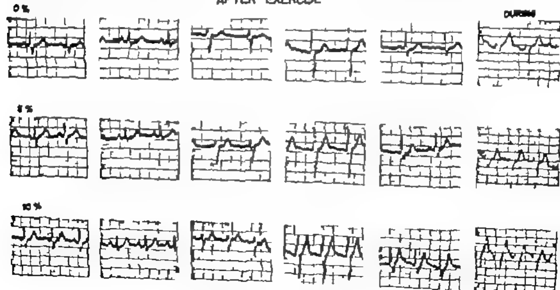


Fig. 2. Electrocardiographic Leads I, II, V2, V4, V6 (of H. S., healthy 52-year-old man with a body weight of 78.3 kilograms) taken in the supine position at rest and after exercise (walking on the treadmill at a speed of 3 m.p.h. at 0, 5, and 10 per cent grades, for 15 minutes), and bipolar frontal-dorsal chest lead taken in the standing position and during walking (eighth to tenth minute). The oxygen consumption per minute per kilogram was 13.4, 16.6, and 25.3 c.c. at 0, 5, and 10 per cent grades, respectively. Changes in the ECG are minor, which is representative for 29 out of 30 healthy men investigated.

Master's two-step test has the advantage of rather general acceptance in North America. The question arises whether its clinical application should be continued or abandoned in favor of physiologically better founded testing procedures. Perhaps in practical application the difference may not be large since most patients with latent coronary insufficiency will show an abnormal response with any type of exercise that reaches a critical value of oxygen consumption. This does not imply that there is a fixed critical value for an individual patient; on the contrary it is quite variable, as is the resting ECG in a patient with coronary insufficiency.[6]

Compared to other types of exercise tests (bicycle ergometer, walking on the treadmill) the step test has the advantage of convenience, economy, and a large body of experience.

It is clear that a greater percentage of abnormal responses will be obtained with an increasing work load but at the same time the risk will be increased. At low work loads the large number of false-negative responses decreases the diagnostic value and this was the reason for doubling the work load in Master's test. The best discriminating load level has never been systematically investigated but clinical experience with a load corresponding to an oxygen consumption of about 1,000 to 1,500 c.c. per minute, as in Master's test, with a duration of 3 minutes has in general been favorable.

II. Types of postexercise ECG changes

Although the ECG changes after moderate (aerobic) work are minor in healthy people, striking changes occur after severe (anaerobic) work —sinus arrhythmia and transient relative bradycardia have been observed, and increased P amplitude, Tp with junctional S-T depression, right axis shift, and particularly a large increase in the T wave, which was not related to positional changes or changes in serum potassium (Fig. 4,A). It was suggested that this response may be due to generalized myocardial hypoxia or possibly to the hemodynamic load. This type of response occurred in patients with aortic insufficiency at a much lower level of work (Fig. 4,A1) frequently associated with an excessive increase in the heart rate. Since these patients have a greater oxygen debt and greater lactate accumulation, the response may suggest that a level of work which is aerobic for healthy people approaches anaerobic performance in these patients, indicating cardiac work insufficiency. The typical response of patients with coronary insufficiency (S-T depression with diphasic or inverted T) is entirely different (Fig. 4,C1) and cannot be reproduced in normal young persons by the most severe exercise. Therefore it is likely due to a different mechanism, i.e., localized myocardial ischemia. Wagman and associates[7] found a correlation between oxygen saturation of the coronary venous blood obtained by coronary sinus catheterization and a positive response to the two-step exercise test.

III. Criteria

Master[1, 14-16] originally gave the following criteria for an abnormal response: depression of the RS-T segment over 0.5 mm. from the terminal part of the P-R interval, change of a positive T wave to a flat or inverted T wave or reversal of a negative T wave, widening of the QRS complex, large Q waves, A-V block (first degree to complete), or arrhythmias.

Most investigators[21-37] using Master's two-step test found that Master's original criteria were too liberal and produced a large number of false abnormal responses. Master increased the load (double Master test) without changing the criteria, thus reducing the number of false-negative responses, and later Master and Rosenfeld[16] also changed the criteria as follows. For a positive test: (1) any RS-T depression of $\geq$ 2 mm.; (2) a junctional (j) depression with QX/QT fraction of 50 per cent or more or with a Q-T ratio of 1.08 or more, or both; (3) ischemic S-T depressions (horizontal or sagging). In contrast, a j depression <2 mm. with QX/QT < 50 per cent or Q-T ratio <1.08 is considered to be negative. The QX/QT ratio was proposed as a criterion by Lepeschkin and Surawicz.[19] X is the intercept of the S-T segment and the base line. Utilization of the Q-T ratio (actual Q-T interval to Q-T$_c$, derived from Bazett's formula[38] $QT = K\sqrt{RR}$ with K = 0.4) is entirely

on empirical grounds. Bazett's formula does not accurately represent the relationship between heart rate and Q-T interval.[31] The Q-T changes depend on the resting heart rate, absolute heart rate during exercise, rate of increase in heart rate during exercise, and decrease in heart rate after exercise. Because of the multiple factors involved, including also considerable variation in measurement, a rather large variation in the Q-T ratio must be expected.

Much attention has been paid to the contour of the RS-T segment.[32] A depressed horizontal or downward-sloping S-T segment is generally called an "ischemic response" because it is the most common type of response in patients with coronary insufficiency. However, how frequently the "ischemic response" occurs in other conditions is not sufficiently known. Three grades have been proposed by Robb and Marks[33] for the horizontal (A, A, A) and the sagging S-T depression (B, B, B). Grading of S-T depression (junctional, "ischemic") and T inversion is also included in the gross clinical classification code employed by this laboratory[34] and has been applied in large samples of working populations (over 12,000 men). However, the S-T and T changes are quite variable, even in repeat tests of individual patients with coronary insufficiency, and sometimes an initially pronounced S-T depression after exercise changes to T inversion with only slight or no S-T depression within 3 to 5 minutes later. An example of this phenomenon is shown

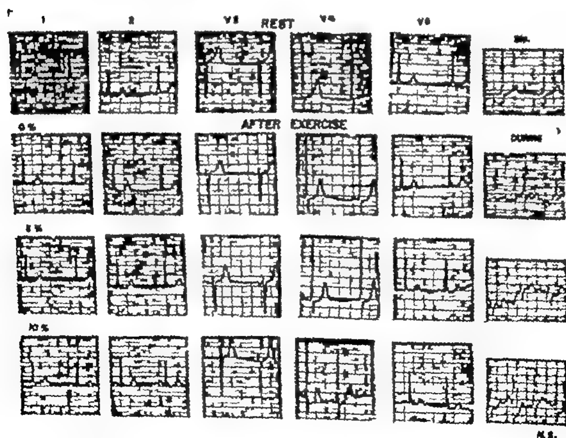


Fig. 3. The ECG shows the exceptional response of M. S., healthy 60-year-old man with a body weight of 81 kilograms; the S-T depression is mainly of the junctional type, particularly in Lead V. Oxygen consumption per minute per kilogram was 14.7, 19.6, and 23.9 at 0, 5, and 10 per cent grades, respectively. The ECG during exercise shows an example of interference which makes S-T evaluation difficult and sometimes impossible.

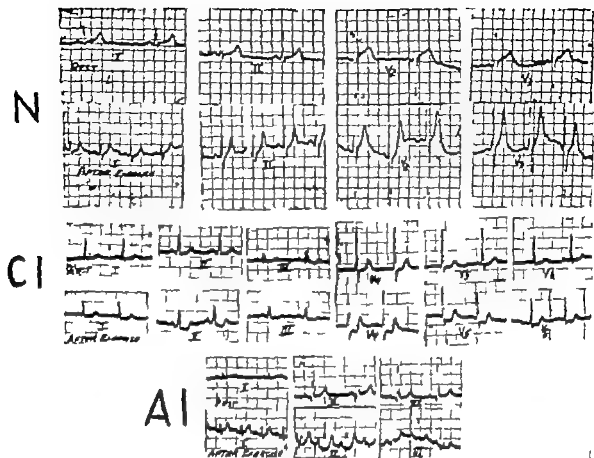


Fig. 4. Electrocardiogram of young man (N) before and after severe exercise (running at speed of 7 m.p.h. at 10 per cent grade). Note the large increase in the T waves. A similar response is shown in patient with aortic insufficiency (AI) who performed a much lower level of exercise. The typical abnormal response of patient with coronary insufficiency (CI) is entirely different (S-T depression with diphasic T). (Reproduced from Simonson, Figure 41, p. 194.)

in Figure 45 of my monograph. Although grading may occasionally be difficult, it works out fairly well in the crude classification of groups, particularly in epidemiological research. It is noteworthy that Master and Rosenfeld[5] in the latest criteria abandoned changes in the T wave. A reversal of an inverted T wave may occur in acute coronary insufficiency, but the diagnostic or prognostic implication of this phenomenon after exercise is not yet established.

The exercise test has been used by many investigators in patients with an abnormal resting ECG. Unfortunately, the criteria for an abnormal exercise test, obtained from a healthy population, do not apply to the response of patients with an abnormal resting ECG. For any individual patient with an abnormal resting ECG it must be carefully considered whether the risk of the test justifies the additional information which may be expected. Only absence of changes (negative test) or pronounced changes can be considered to be significant in patients with an abnormal resting ECG. On the other hand, the exercise test is of particular value when the resting ECG is borderline or when the history is equivocal, for objective documentation of suspected coronary insufficiency.

The evaluation of criteria rests on the ST-T changes. Other abnormal changes (such as A-V block, bundle branch block, arrhythmias) are too rare for statistical evaluation, although they may be of importance for the individual patient. Lamb

and Hiss[33] have recently shown that premature beats have no diagnostic significance: they may appear or disappear in exercise.

IV Specificity

The electrocardiographic exercise test usually has been applied to detect coronary insufficiency and the results (positive or negative) are interpreted accordingly. Consequently, the exercise test has been mostly applied to patients suspected of having coronary artery disease. Thus most samples are so highly preselected that it is difficult to investigate the specificity of the exercise test for coronary artery disease.

Indirect evidence for nonspecificity is an appreciable number of false-negative and false-positive tests, and this will be discussed in Section V. Positive exercise tests have been reported during recovery from infectious diseases,[36,37] in congenital heart disease, anemia, thyrotoxicosis, mitral stenosis,[38] neurocirculatory disorders, vasoregulative asthenia (Sydstrand[?]) and in normal women.[39] The largest and most thorough investigation is the comparison by Hellerstein and associates of the single Master two-step test in 100 patients with a confirmed history of previous myocardial infarction and in 9 patients with rheumatic heart disease (RHD). The patients with RHD were subdivided into 4 with and 50 without digitalis medication. For evaluation, the criteria proposed by Master (original and revised), Myers and Talmers,[?] Lepeschkin and Surawicz,[17] and their own, including vectoral changes, were used. In addition, the S-T depression was graded. The incidence of abnormal responses ranged from 18 to 48 per cent according to the various criteria. There was no significant difference in the incidence of abnormal responses between patients with rheumatic and those with arteriosclerotic heart disease by any of the various criteria used. The incidence of abnormal responses increased with the clinical functional severity of the disease and was not related to etiology, age, or digitalis medication. The abnormal response in conditions other than coronary artery disease may still be an effect of a functional (relative) coronary insufficiency produced by the increased load in a heart with some myocardial damage due to latent myocarditis, toxic effects, or other causes.

V Diagnostic value

The evaluation depends not only on the ECG criteria but also on sample selection and on the purpose of the exercise test, whether it is used for group differentiation (epidemiological studies, life insurance material) or for diagnosis in the individual patient, for specific diagnosis of coronary artery disease (as is most frequently the case) or for demonstration of nonspecific abnormality not detectable in the resting ECG. Furthermore the separation between normal and abnormal responses depends on the clinical as well as the statistical criteria used.

Perhaps the best over-all criterion is the number of abnormal exercise responses in addition to the number of abnormal ECGs at rest found in unselected large population samples. In the experience of this laboratory and associated studies in over 12,000 exercise tests in men in working populations of the United States and several European and Asiatic countries, a substantial number of abnormal responses to exercise is always found among men with a normal resting ECG. In such population groups the number of abnormal ECGs may be doubled if an exercise test is used. There is, however, a variation between abnormal ECGs at rest and after exercise in different populations. A greater frequency of abnormal responses to exercise may be expected in populations with a high prevalence of coronary atherosclerosis (i.e., with a greater number of persons with latent coronary insufficiency). The prevalence of coronary heart disease is high in the United States. In two samples of United States population, 300 sedentary men under observation at this laboratory for 16 years and 3,000 railroad employees,[?] the exercise test added 50 per cent of abnormal ECGs to the number of abnormal ECGs at rest. In a random sample of 1,591 men in Finland, an ischemic ST-T depression was present at rest in 2 subjects and only after exercise in 26 subjects, adding nearly 100 per cent to the number of men to be classed as abnormal.[?]

In a follow up study of 756 clinically un selected business executives by Brody 22 had an abnormal resting ECG and 280 (i e 13 times more) had an abnormal exercise response on the basis of Master s original criteria subsequent clinical coronary artery disease developed later in 11 4 per cent of these men Of 476 subjects with negative tests only 4 2 per cent developed coronary heart disease in the follow up However 69 5 per cent of 23 patients with an ischemic response developed manifest coronary disease. This is a significant group differentiation but there is too much overlap to permit the accurate diagnosis or prediction of coronary artery disease in individual patients.

These studies indicate that the over all diagnostic value of the ECG response to exercise for the detection of heart disease exceeds that of any other electrocardiographic procedure (ancillary leads vector cardiogram) used in addition to the routine 12 lead ECG

Approaches for evaluation of the diagnostic value are the comparison of positive and negative exercise tests (1) in apparently healthy control groups and in patients with documented heart disease and (2) the follow up mortality or development of clinical coronary heart disease among persons with positive and negative tests. All groups studied are highly preselected since the exercise test is usually performed only in patients with suspected or even proved coronary artery disease

The largest follow up study with mortality as the criterion was performed by Robb and associates[8,44] on 836 former patients of Walter Reed Hospital who were suspected of having coronary artery disease and 379 life insurance applicants The over all death rate of patients with a positive (double Master s) exercise test was about 5 times and the coronary death rate about 7 times, higher than that of patients with a negative test The most important criterion was an ischemic S-T depression junctional S-T depression and a T inversion without S-T depression was found to be of little if any significance in the prediction of mortality In these authors most recent study[47] the insurance material was considerably enlarged to cover 1,236 applicants with an average follow up of 5 years. A history of chest pain was present in 57.3 per cent and healed myocardial infarction or an abnormal resting ECG in 30 per cent The exercise test was negative in 54 8 per cent whereas ischemic S-T depression was found in 16 per cent junctional depression in 27 3 per cent and T wave changes or arrhythmias in 2 5 per cent The mortality from all causes on the basis of 23 deaths was 26 per 1 000-person years of observation in cases of ischemic S-T depression or 4 times that of cases in which the response was negative (21 deaths) and this difference was statistically significant The death rate from coronary heart disease (21 deaths) in the ischemic group was 6 times higher than that in the group with a negative response With increasing depth of ischemic S-T depression there was a progressive increase in total and coronary mortality however the number of deaths in the three subgroups (S-T depression <1 mm from 1 0 to 1 9 mm 2 mm or more) was too small to give anything more than an indication of this trend

The mortality rates in patients with S-T junctional depression and in patients with a negative exercise test were not significantly different in fact the mortality was somewhat less in the cases of junctional depression The number of cases of isolated T changes was too small for evaluation The authors concluded that the response to exercise is a better indication of significant coronary impairment than the history or other indications. The actual number of deaths in patients with ischemic S-T depression (although significantly greater than expected mortality) is too small for a mortality prognosis for the individual patient except in very general statistical terms i.e in categories of relative mortality risk

The absence of a correlation of post exercise J depression to mortality in Robb and Marks sample is somewhat surprising since a junctional S-T depression with an upward-sloping S-T segment and often a reversal of a previously inverted T wave may occur in spontaneous attack of angina pectoris Friedberg and associates found the junctional type of depression (> 0.5 mm) in 10 of 29 patients with typical angina pectoris and the ischemic type

of S-T depression was more common than J depression in nonanginal patients with a false positive test. Master and Rosenfeld[3] found that 30 per cent of the patients with J depression after exercise had organic heart disease. This is a substantial percentage. A prolonged QX/QT ratio or Q-T ratio separated the J depression due to organic heart disease and the functional J depression. However, Friedberg and associates agree with Robb and Marks[5] that the QX/QT ratio and the Q-T ratio are worthless for differentiation between a positive and a negative response but disagree in the over-all evaluation of the exercise test. Friedberg and associates concluded that the exercise test contributed little to a careful clinical examination in the detection of coronary heart disease. However, Robb and Marks used mortality as a criterion in a follow-up study, whereas Friedberg and associates based their conclusions on an independent diagnosis of coronary heart disease.

The normal limits (95 or 98 per cent) are most frequently used in clinical application) should be determined on the basis of the frequency distribution of the exercise response for the various ECG characteristics in a proper sample of the healthy population. No such study has been reported. Instead, entirely arbitrary screening levels have been proposed; the percentage of normal and abnormal responses in respect to these screening levels have been reported. Therefore, it is not surprising that the results of different investigators are at variance. Apparently satisfactory normal limits were obtained by Wener and associates[19] with 311 healthy persons, of whom only 3.2 per cent in the single Master test and 7.1 per cent in the double-step test showed an S-T depression that exceeded 0.5 mm. Isolated (without S-T depression) T inversion was not seen. Leeds and Kroopf[37] found an abnormal response in 8.7 per cent of 69 normal women who were under 35 years of age. Lepeschkin and Surawicz[29] found that the overlap between positive and negative responses in 243 healthy subjects was so large that only in men from 19 to 29 years of age was a negative test diagnostically meaningful. The incidence of negative tests in healthy men over 56 years of age was only 1 per cent and it was even lower (42.3 per cent) in women over 56 years of age. The least degree of overlap (94 per cent positive tests in patients; 23 per cent positive in healthy persons) was obtained by a combination of criteria (T inversion or J depression > 0.75 mm. with QX/QT ratio greater than 50 per cent, or 0.5-mm. S-T depression lasting 2 minutes or more), but even with this combination the number of false-positive tests is too large for clinical application in individual patients.

Master and associates[11,17,34] have always stressed negative rather than positive tests. A false-negative test occurred only in about 5 per cent of the patients with coronary heart disease, and the authors stated that a negative test practically excludes organic coronary disease. Selection and matching is difficult with samples of the healthy population but nearly impossible with samples of patients; therefore, different distributions should be expected for the various samples analyzed by different authors.

Friedberg and associates recently reported results of one of the best controlled series. Clinical history and symptoms and the double two-step test were investigated by different physicians and the ECGs were interpreted by two or three physicians ("double-blind evaluation") in 100 consecutive ambulatory patients. As expected but never before so clearly demonstrated, progressive grading of S-T depression diminished the number of false-positive responses but increased the number of false-negative responses. None of the various criteria used (including those recently proposed by Master and Rosenfeld[3]) gave a satisfactory differentiation between patients with angina pectoris and other patients, and the authors conclude that angina pectoris can be better diagnosed or excluded by clinical information than by the exercise test.

Most observers, however, believe that the exercise test has a definite value in the early recognition of coronary heart disease. Among recent investigators, Dimsdale, in a 5 year follow-up study of 153 railroad employees (most—111—with an abnormal resting ECG), found the incidence of myocardial infarction to be about 3 times and

the mortality to be about 2 times greater in patients with an ischemic response to exercise (40 ascents as rapidly as possible with comfort) than in patients with a negative response. He comments on the difficulty of evaluating the resting ECGs with an S-T depression Lloyd Thomas[40] gave a cumulative listing of various abnormal changes in 187 patients who had an abnormal resting ECG but who were able to engage in considerable physical activity The most common changes after exercise (2-step test not rigidly standardized) were J and S-T segment depression (usually combined) but in several cases, isolated T inversion or reversal of negative T waves developed Transient ventricular fibrillation occurred in one of his patients. Lloyd Thomas concluded that the exercise test is a valuable additional diagnostic procedure but agrees that a normal response does not exclude coronary artery disease

In most recent investigations S-T changes have been emphasized rather than isolated (i.e without S-T depression) T changes but from statistical considerations, T inversion would be just as abnormal although its clinical significance may be different Russek[44] believes that T inversion should not be disregarded since it may occur in spontaneous attacks of angina. In Figure 47 of my monograph [8] an example is shown of spontaneous T inversion in Leads V_1 through V_6, 2 months after a postexercise J depression of 2 mm when the resting ECG was still normal

Attempts have been made (first by Master and associates[4]) to differentiate false and true positive tests by the use of ergotamine and other drugs. A review of the literature led me to conclude that this procedure is of questionable merit It has been used on an experimental and exploratory basis by only a few investigators and *no recent reports could be found*

Most authors have used the exercise ECG test for specific diagnosis of coronary artery disease It appears logical to assume that an abnormal response occurs more often in coronary heart disease than in other conditions but large-scale studies are still needed to clarify this situation. It may be assumed that the results and conclusions in samples with a low prevalence of coronary disease and higher prevalence of other conditions would be different

In view of the different criteria different sample composition etc. the existing controversy is perhaps less surprising than the general agreement of most of the authors about the potential value of the exercise test.

VI. Response during and after exercise

Significant electrocardiographic changes may occur occasionally during work and disappear rapidly in the recovery period[44,45,46] so that they are missed in the postexercise ECG On the other hand as re-emphasized by Robb and Marks[47] the largest changes are occasionally seen several minutes after exercise rather than immediately The development of ECG changes *during* exercise depends of course on its duration and load In our experience with 30 screened healthy men the changes during exercise were minor

Interference by muscle action currents or electrode motion are a problem in taking the ECG during exercise. Usually bipolar (frontal-dorsal) chest leads give satisfactory records. Abarquez and associates[48] used lead connections which gave similar (but not identical) records to V_4, V_5, V_6, V_7 leads. Since legs and arms act as linear conductors, a modified Wilson terminal with electrodes placed near the shoulder and on the hip will give records quite similar to precordial V leads and with less interference. We found that bipolar chest leads were satisfactory at moderate work loads (walking on the treadmill 3 m.p.h 5 per cent grade) but at a load close to the aerobic capacity interference (probably due to sweating) developed after several minutes of work. The telemetering technique (pioneering work done by Holter[44]) eliminates interference due to the *pull of cables. However fixation of the* cable by tape on the shoulder will reduce the pull substantially and it is not certain that this is the major source of interference.

The main question whether there is a significantly greater number of abnormal responses *during* exercise than after exercise cannot yet be reliably answered Without exception all investigators have used criteria for the postexercise ECG

response to analyze changes *during* exercise a questionable procedure. Even on this basis there has been no statistical evaluation in any of these studies reported. Although impressive changes have been demonstrated in individual patients during exercise,[37-41] the diagnostic value cannot be evaluated on this basis.

Levenson and Sparkman[39] using walking on the treadmill (150 feet per minute, 10 per cent grade, for 10 minutes or until development of symptoms) found S-T depression in 21 patients and T inversion in 24 patients during exercise, whereas these changes occurred during recovery in 16 and 18 patients, respectively. In view of the large group (366 patients), the difference in frequency approached the 5 per cent level of statistical significance. Since all but 7 per cent of this group had organic heart disease, the percentage of abnormal responses (during as well as after exercise) is relatively small as compared to other series.

The largest material has been collected by Bellet, Deliyannis, and Eliakim.[40] They compared ECG changes during and after exercise (Master's *double* test) in 127 normal subjects, 14 cardiac patients, and 22 patients with miscellaneous (noncardiac) diseases. The incidences of J depression in the normal group during and after exercise (13 and 12 per cent) were similar, and the number of ischemic S-T depressions was too small for statistical evaluation. In 43 cardiac patients with normal resting ECG, changes only during exercise (10.5 per cent) were somewhat more frequent than changes only after exercise (6 per cent), but these differences did not reach the level of statistical significance. Bellet and associates in another study on 70 patients with coronary artery disease (using the *single* Master two-step test) found changes during exercise in 37 (53 per cent) and after exercise in 24 (34 per cent). This difference in frequency is significant at the 5 per cent level. It is surprising that the results in this second group with the single Master exercise test showed a better differentiation than did those in the first group with the double Master test, but this may be due to the different composition of the group.

*We wish to thank Miss Jean LaRivere for the statistical evaluation.

In 135 apparently healthy men from 17 to 64 years of age, Bellet and associates[41] used a bicycle test (20 to 25 miles per hour for 3 minutes, and in a few subjects for 4 to 10 minutes). The resistance was not stated, so that the exercise load is not precisely defined, but it was considered to be strenuous. Of a total of 34 abnormal and probably abnormal responses (24.8 per cent), [redacted] per cent were detectable during exercise and 65 per cent were detectable after exercise. The difference between these values (82 and 65 per cent) does not quite reach the level of statistical significance. The fact that 20.4 per cent of this group of healthy men had an abnormal response means that either the group used is not representative of a healthy population or the criteria used are not valid.

One may say that the results of Bellet and associates[40, 41] suggest a greater yield of positive responses but do not provide conclusive evidence for the diagnostic superiority of the ECG during exercise over the postexercise ECG.

Ultimately, the value of changes during exercise has to be demonstrated in follow-up studies. The subject clearly deserves further exploration before wider clinical application is made.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Evaluation of angiotensin as a therapeutic agent

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It is believed that renin, when secreted by the renal juxtaglomerular cells, activates circulating angiotensin I, an alpha 2-globulin decapeptide complex which, through enzymatic degradation, becomes angiotensin II. Angiotensin II, henceforth called simply *angiotensin*, is an octapeptide which derives most of its medical interest from its marked pressor activity. It was purified in 1956 and synthesized a year later.

Angiotensin amide is now available for clinical use. It exerts its pressor action primarily by increasing the peripheral resistance through direct stimulation of arteriolar smooth muscle. An indirect effect via arteriolar innervation has also been postulated.

Within a few minutes after this agent is administered intravenously, it is broken down in the blood to inactive peptides. In normal individuals who receive single large doses, the pressor response is accompanied by a decrease in cardiac output. A mild reflex elevation of venous pressure caused by venoconstriction occurs; this is abolished by anesthesia and atropine and is less intense than that seen with l-norepinephrine. Other effects include a gradual rise in pulmonary and right atrial pressures, inconsequential change in coronary blood flow, and decrease in renal plasma flow, glomerular filtration rate, and excretion of sodium.

If factors that control the secretion of aldosterone are held constant, angiotensin can promote a 32 to 250 per cent increase in the secretion of aldosterone by direct stimulation of the zona glomerulosa of the adrenal. This may not be seen in some decompensated cirrhotic patients whose adrenals may be producing aldosterone maximally.

Although present in free form, the normal blood content of angiotensin has not been accurately measured. In certain hypertensive patients a slower rate of degradation may explain the reported higher blood levels and the increased total exchangeable pool of angiotensin. The hypertensive patient seems to possess an increased sensitivity to the agent, which has led some to speculate as to the possible existence of a genetic enzymatic defect in this disease. Utilizing the observation of hypersensitivity to angiotensin, a test for the potential detection of *pre-hypertensive* subjects has been suggested. Duration of the skin blanching produced by the intradermal injection of 0.1 microgram of angiotensin in saline is said to be more pronounced in the hypertensive than in the normal sub-

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ject, but because of the overlap in results this test cannot be considered to be reliable at present.

Angiotensin has been suggested for use in most forms of shock in which a pressor agent is indicated. It is presently not recommended for the treatment of shock in acute myocardial infarction. The drug is 5 to 10 times more potent than levarterenol but, unlike the latter it can be given alone intravenously intramuscularly or subcutaneously without producing local tissue damage. However only the intravenous route has been recommended clinically. In hemorrhagic shock, the response to angiotensin is less likely to produce adverse electrocardiographic changes than is that to l-norepinephrine.

As with renin a linear dose-pressure response curve is observed When large doses are infused an initial arterial pressure peak is followed by a partial decline without alteration of the responsiveness to l-norepinephrine. The hypertensive effect is nullified by papaverine, adenosine triphosphate, theophylline ethylenediamine and chlorothiazide but not by adrenolytic agents. Interestingly hexamethonium pentolinium and tetraethylammonium enhance the vascular response to angiotensin Tachyphylaxis has not been a problem The drug is costlier than levarterenol.

The cirrhotic patient with ascites may exhibit a reduced pressor response to angiotensin similar to that seen with norepinephrine. Also pregnant women are less sensitive to the vasopressor effect of angiotensin the response returns to normal in the puerperium In the severe hypertensive or decompensated cirrhotic patient the infusion of pressor doses of angiotensin can produce increased diuresis and natriuresis while depressing the secretion of aldosterone

These varied actions of angiotensin are most interesting Other than as a valuable research tool its clinical use should be considered to be premature. A recent clinical report on patients in shock described a reduction in cardiac output and urinary flow rate which was measurably greater than that produced by several other pressor drugs, in dosage that had a comparable effect on the blood pressure. This is presumably due to its lesser venoconstrictive effect. Thus it should be reserved for trial in shock that does not respond to the well-established pressor agents It is for these reasons that details on dosage and clinical usage have been omitted deliberately in this discussion A better understanding of its clinical pharmacology and mechanism of action and further controlled clinical trials will ultimately establish the true therapeutic worth of this fascinating drug

Nonproprietary name, angiotensin Trade name Hypertensin.

Annotations

Inorganic phosphates in acute renal failure

Not much is know bout the phosphates in acut renal fail re Tw preliminary obser tions—the pat ern of the rinary excretion of phosphates and the signifi nc of the serum level of inorganic phosphorus are presented belo showing their p tible importan in linical medicine in ses of acut renal failure

Wherea normal subject the tio of phosphat le ran to cre t nine clear nc (Cp Ccr) depend upon the level of the serum phosphorus, in patient in renal f ilure seems t be independent of it This r tio is ised the e of hronic irreversible renal f l re A the glomerular filtration rat (GFR) decre ses h ad nc ng enal disease the ratio Cp C ncre ses This is due t the lmost complete essation of tubular eabsorption of the filtered phosphates nd quantitative tra fer of them t the rine The excret on of phosphorus becomes higher than pec ed the particula level of phosphorus f und in he serum nd no longer proport onal The learanc ratio remains high even fter he concent t on of phosphoru the serum has been reduced by diet lo in phosphates The serum phosphoru does not begin t rise ntil he GFR is less tha 15 20 ml per minut The increase in the Cp C r dd be in erpreted ttempt t minimize th retent on of phosphates inspite of decreased renal func on

The mechanism h h underlies the excretion of a incre ing fraction of he filtered phosphat is attributed t econdary hyperparathyroid sm nd t adapt h nges induced by he uremic tat From these fact and interpr tat ons, it follow hat in acut renal f lure the patient ha had no time t dev lop hese ad ptiv hanges This is nderstandable since ac renal f ilure is disease entity wh h is d fferent l all ph siologically nd pathologically from hronic renal f ilure nd is theref re expected l ha in different manner For these re son ha in estigated the excretion of phosph tes in the dable cases of acut reversible renal f ilure

Six patient who were ffering from ac t reversible renal f ilure were in est ga ed. Cle nces of ph phates nd cre tin e ere determined in the 24 hour urine llect ons All these patien were strict dietary regimen f oral art h dra es nd intra en glucose wi It w f und that during the oliguric phase hen the Ccr w less tha 10 to 12 ml per minut the Cp Ccr w lo he normal or even in the w known l ra ge Th t fell in di tinctly different rea of the graph when compared with that of ases of hronic renal f ilure I 4 cases which were followed up further it was f und that with improvement n the Ccr reached 10 t 15 ml. per minut the Cp rose steeply nd even surpassed the Ccr reaching bsolute lev ls ell abov the accepted normal range Thus the Cp/Ccr ratio, which was low during the oliguric tage w also raised. Although this pattern was consistent nd seems t to ha e been genuine further investigations re necessary t confirm it

Since our preliminary communication, 5 more patient with acute reversible renal failure hav been ailable and ha been examined daily in the same way Their Cp/Ccr ratios during the oliguric phase were agreement with our previous findings nd were in the range of 0 23 to 0 46. This ratio increased w th the onset of the polyuric phase nd reached 0 97 in one of them whom w had the opportunity t follow up

The finding of low lues of Cp/Ccr in acute reversible renal failure during the oliguric phase complemented by the high alues of Cp/Ccr found in hronic renal failure seem t offer an easy and practical test for the differentiation of these tw conditions. Such differentiation is of great clinical importanc I the obscure cases of renal failure in patient with inadequat histories when referred for dialyses. The limitations of such test ill probably be clarified by further experience

The hyperphosphaturia during the polyuric phase of acute enal f ilure seems to be nalogous t the observation of Conelly nd sociates[4] in the neonatal period. They found hyperphosphatemia and h popho-phat ria with relati insensiti ity to I ara-thormone in the fir t day of life. Hyperphosph turia ppears on the third day of life nd lready in the first few day ma ked enhanced responsiveness t the hormone is seen— thirtyfold increase I ph phaturia in response to the same dose of the hormone compared to the first day of lif The hyperphosphaturia which ppears with maturity of the kidney in the arly neonatal per l seems t be simila to the hyperphosphaturia of the recovering kidney in the case of acut renal failure

I acut ren l f il re the level of bl d urea i sed the usual indicator for the optimum time f r dialysis. However the lev l of bl l urea depend pon ma y fact rs such the int k of itrog ene s material the pacity of it dialy is by the st f l kidney the t l de nd there being

tion of blood from viscera or hematomata. It seems, therefore, that the blood urea level cannot always serve as a reliable guide to the severity of the uremia. Urea diffuses rapidly across the cell membranes and is easily removed by dialysis. On the other hand, phosphates are slowly diffusible, and their level in the plasma can hardly be reduced after the first 3 or 4 hours of dialysis. Thus, in the more severe cases of acute renal failure which require more than one treatment with the artificial kidney, a differential correction of the uremic state is developed. In these cases, therefore, the blood urea level can no longer be regarded as indicative of the accumulation of other biochemical substances.

According to our experience, the serum inorganic phosphorus can be used to complement the blood urea level in assessing the patient's clinical condition. Those patients who developed the severe symptoms of uremia, such as severe acidosis and especially gastrointestinal bleeding, had had a serum phosphorus of more than 9 or 10 mg. per cent. In the usual case the hyperphosphatemia is associated with a high blood urea. However, we found a better correlation of the severity of the clinical condition with the level of serum inorganic phosphorus than with the level of blood urea. This was true especially in the patients who were under strict dietary therapy or repeated artificial dialyses. In such cases, therefore, we believe that the blood urea level is not a reliable guide to the patient's clinical condition, and that the level of serum inorganic phosphorus must be used as the indicator for the optimum time for artificial dialysis, and should not be allowed to rise beyond 9 or 10 mg. per cent before artificial dialysis is performed, no matter what the level of blood urea is.

The difficulty of reducing the level of the serum inorganic phosphorus by artificial dialysis, especially in those in whom repeated dialyses are necessary, is well known. We found that those patients who benefited most from the artificial dialysis per se were those whose serum phosphorus was decreased considerably by the procedure. Three severely injured patients in whom the serum phosphorus did not decrease substantially by what is considered to be adequate dialyses, with the help of the Kolff-Watschinger Twin-Coil Artificial Kidney, remained in a severe condition and died. The role of the complexed phosphates in such patients is not known.

Even though the blood urea level is a good guide to the optimum time for dialysis in the usual case, it seems to us that the serum phosphorus level must also be taken into consideration if the patient's clinical condition is to be assessed objectively, especially in those with the more severe cases of acute renal failure who need more than one dialysis or who have a more protracted course.

Finally, the following statement made by Giebisch must be quoted: "The recent observation made by Walser, according to which only 53 per cent of plasma phosphates are present as 'free' ions, the rest being either protein-bound or complexed, may have an important bearing on future studies concerned with the mode of renal phosphate excretion." This statement must be taken seriously in future studies of the significance of phosphates and the manner of their excretion in renal failure.

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Fibrillation

Cardiac fibrillation, the rebellious palpitation, has been recognized by medical men in its various forms for a couple of centuries. Atrial fibrillation, which although compatible with many years of useful life, had to be accepted a generation ago as permanent disability, can usually be terminated by quinidine or procaine amide if this is considered to be desirable. Ventricular fibrillation is rapidly fatal, and although it may be obedient to the techniques of the cardiac surgeon, remains a hazard

Annotations

Inorganic phosphates in acute renal failure

Not much is known about the phosphates in acute renal failure. Two preliminary observations—the pattern of the urinary excretion of phosphates and the significance of the serum level of inorganic phosphorus—are presented below, showing their possible importance in clinical medicine in cases of acute renal failure.

Whereas in normal subjects the ratio of phosphate clearance to creatinine clearance (Cp/Ccr) depends upon the level of the serum phosphorus, in patients in renal failure it seems to be independent of it. This ratio is raised in the case of chronic irreversible renal failure. As the glomerular filtration rate (GFR) decreases with advancing renal disease, the ratio Cp/Ccr increases. This is due to the almost complete cessation of tubular reabsorption of the filtered phosphates and quantitative transfer of them to the urine. The excretion of phosphorus becomes higher than is expected at the particular level of phosphorus found in the serum, and is no longer proportional to it. The clearance ratio remains high even after the concentration of phosphorus in the serum has been reduced by a diet low in phosphates. The serum phosphorus does not begin to rise until the GFR is less than 15 to 20 ml. per minute. The increase in the Cp/Ccr ratio could be interpreted as an attempt to minimize the retention of phosphates in spite of decreased renal function.

The mechanism which underlies the excretion of an increasing fraction of the filtered phosphate is attributed to secondary hyperparathyroidism and to "adaptive changes induced by the uremic state."[1] From these facts and interpretations, it follows that, in acute renal failure, the patient has had no time to develop these adaptive changes. This is understandable since acute renal failure is a disease entity which is different clinically, physiologically, and pathologically from chronic renal failure, and is therefore expected to behave in a different manner. For these reasons, we have investigated the excretion of phosphates in the available cases of acute reversible renal failure.

Six patients who were suffering from acute reversible renal failure were investigated. Clearances of phosphates and creatinine were determined in the 24-hour urine collections. All these patients were on a strict dietary regimen of oral carbohydrates and intravenous glucose only. It was found that during the oliguric phase, when the Ccr was less than 10 to 12 ml. per minute, the ratio Cp/Ccr was in the normal or even in the subnormal range. This ratio fell in a distinctly different area of the graph when compared with that of cases of chronic renal failure. In 4 cases which were followed up further it was found that with improvement, as the Ccr reached 10 to 15 ml. per minute, the Cp rose steeply and even surpassed the Ccr, reaching absolute levels well above the accepted normal range. Thus, the Cp/Ccr ratio, which was low during the oliguric stage, was also raised. Although this pattern was consistent and seems to us to have been genuine, further investigations are necessary to confirm it.

Since our preliminary communication, 5 more patients with acute reversible renal failure have been available and have been examined daily in the same way. Their Cp/Ccr ratios during the oliguric phase were in agreement with our previous findings and were in the range of 0.25 to 0.46. This ratio increased with the onset of the polyuric phase and reached 0.97 in one of them whom we had the opportunity to follow up.

The finding of low values of Cp/Ccr in acute reversible renal failure during the oliguric phase complemented by the high values of Cp/Ccr found in chronic renal failure seems to offer an easy and practical test for the differentiation of these two conditions. Such a differentiation is of great clinical importance in the obscure cases of renal failure in patients with inadequate histories when referred for dialysis. The limitations of such a test will probably be clarified by further experience.

The hyperphosphaturia during the polyuric phase of acute renal failure seems to be analogous to the observations of Connelly and associates[2] in the neonatal period. They found hyperphosphatemia and hypophosphaturia with relative insensitivity to Parathormone in the first day of life. Hyperphosphaturia appears on the third day of life and already in the first few days a markedly enhanced responsiveness to the hormone is seen—a thirtyfold increase in phosphaturia in response to the same dose of the hormone, as compared to the first day of life. The hyperphosphaturia which appears with maturity of the kidney in the early neonatal period seems to be similar to the hyperphosphaturia of the recovering kidney in the case of acute renal failure.

In acute renal failure, the level of blood urea is used as the usual indicator for the optimum time for dialysis. However, the level of blood urea depends upon many factors, such as the intake of nitrogenous material, the rapidity of its dialysis by the artificial kidney, the catabolic rate, and the reabsorp-

cells, and the *maintenance* of these differences is assisted by selective restrictions to the free passage of ions by the cell membranes. The intracellular potassium concentration of cardiac muscle is over thirty times higher than that of the plasma,[14] and a negative intracellular potential of 90 mv. would be required if such a difference in concentration were to be *maintained at equilibrium*. The ratio of extracellular to intracellular sodium is more difficult to measure accurately because a small error in the estimate of the distribution of water between the intracellular and extracellular compartments greatly affects the calculated intracellular sodium concentration. However, if the high external sodium were to be in equilibrium with the low intracellular sodium, a *positive* intracellular potential of 30 to 40 mv. would be required. During the spike of the ventricular action potential, sodium conductance increases vastly so that sodium-carried positive charge crosses the membrane with such rapidity that the intracellular potential goes temporarily positive (the "overshoot") to a value not far from the theoretically possible sodium equilibrium potential of about +35 mv.

In ventricular and in skeletal muscle at rest the intracellular potential measured with microelectrodes is, in fact, about −90 mv., i.e., close to the potassium equilibrium potential. A sudden removal of any restraint to the passage of potassium ions through the membrane would not, therefore, create any change in the resting potential, since an increase in the flux of potassium ions, which were already at equilibrium, would be equal in both directions and would not lead to any transfer of charge. If, however, the intracellular potential had been displaced from −90 mv., then an increase in potassium permeability could accelerate the return of the potential toward this resting value. It is believed that, in nerve,[16] such an increase in potassium permeability occurs in the wake of the "spike" of the action potential, and thus speeds up the restoration of the resting potential, with the result that a train of action potentials can be accepted at high frequency.

In the atrium, however, although the intracellular potassium concentration is as high as that in the ventricle, the observed diastolic resting potential is only 75 to 80 mv., i.e., *below the potassium* equilibrium potential. There is much evidence that parasympathetic activity specifically increases potassium permeability,[16,17] especially in the sinoatrial node, thus hyperpolarizing the membrane and opposing the development of pacemaker impulses. The membrane potential is locked, as it were, by the high flux of potassium at a level nearer the potassium equilibrium potential (−90 mv.), so that impulses from the physiologic pacemaker are less frequent or are cut off altogether. If, however, impulses do get *through as from an ectopic focus, they travel faster* and can occur more frequently, since the high potassium permeability speeds up the process of repolarization after a spike, and the likelihood that fibrillation will develop is increased.

Conversely, it is evident that any drug which slows down the rate of repolarization, thus prolonging the absolute refractory period by delaying the time at which the membrane is sufficiently repolarized to become again excitable, will be antifibrillatory.[18] Experiment has shown, however, that quinidine, procaine amide, and other antifibrillatory drugs do not act in this way.[19] They greatly slow down the rate of entry of *depolarizing current during the rising phase of the action potential*, i.e., *they* oppose the *formation* of impulses. Such an effect might readily be produced by these drugs if they interfered at some point with the mechanism by which the metabolically released energy of the cell can be utilized to extrude sodium ions, so that intracellular sodium would accumulate, and the concentration gradient available for the development of a spike would be reduced. Here again, however, the evidence is[14] that the intracellular sodium is unaltered or even reduced in the presence of antifibrillatory drugs, so that they must interfere in some more direct way with the process by which positive charge is transferred into the cell to create a spike. Quinidine and similarly acting antifibrillatory compounds have little effect on the lethal dose of cardiac glycosides.[7]

The great interest of Nethalide is that it could act in a different way, and its antifibrillatory activity may be connected with the removal of excessive sympathetic drive. However, the mode of action of the sympathetic is much less clear than is that of the parasympathetic. The higher frequency of formation of impulses in the S-A node under sympathetic drive could be due to a decreased potassium permeability[20] (i.e., the opposite of vagal action), but direct evidence for this is slight, and considerable sympathetic effects are produced in the absence of any prolongation of the action potential, such as would be expected if potassium flux was decreased. Yet it is clear that alterations in the differential permeability of ions must be involved, even if only indirectly,[21] in the action of drugs which affect both normal and abnormal cardiac rhythms. There is still a long road to be traveled before a full explanation of the influence of sympathomimetic and sympatholytic drugs on the formation of impulses is achieved. Nevertheless, recent work has clarified the scene and has indicated the direction[22] in which research is most likely to yield a better understanding of the mechanism of fibrillation and of the mode of action of drugs on the heart.

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The emergency reaction in thrombogenesis and in atherogenesis

Cannon emergency reaction"[1] is part of the mechanism of defense against loss of blood which has evol ed over millions of years of daily trauma. Cannon description ncluded the effects of epineph rine in constricting blood vessels of cutaneous and splanchnic territories *while dilating those of somatic* and cardiac muscle, and also enhancement of blood coagulability He gave this complex process the name emergency reaction because he believed that its purpose as an acti counterreaction to bleeding as well as t the hypotension of shock, and preparation for fight or flight.

Almost quarter of century after Cannon description, we ha described two additional pro tectiv mechanisms against bleeding also induced by epinephrine nd not by norepinephrine, which occur t the same time as Cannon emergency reaction. These are the (1) platelet sticking reac tion, and (2) filling reaction of arterial walls.

Platelet sticking reaction is the name has given t the acute appearance of adhesiveness of ascular endothelial cells to platelets, which can eventuat in the ggregation of platelets and the formation of white thrombi.

The *fill g reaction* (which has also been called edematous arterial reaction) consists of the noticeable increase in volume of extracellular space in the media and subendothelium of rteries. These spaces become filled ith plasma-like material hich stains light violet by metachromatic stain with toluidine blue. The reaction occurs only in arteries ith thick media equipped with characteris tically large extracellula spaces, nd has not been observed in arterioles or eins The mechanical effect of the filling reaction, an effect hich we believ to be importa t is t increase the volume of the arterial wall with spongy material. This increase and change in character of the arterial wall suggest an interesting mechanical analogy ith the method used for automatic sealing of punctures in the walls of some pressurized, high-altitude aircraft the dan ger of the loss of ir through the walls of the cabin

because of the higher pressure inside than outside the cabi t high altitudes is carefully prevented by filling of spongy rubber inside the walls for automatic sealing of punctures. The arterial lumen is alway filled by blood with pressure which is over 100 mm. Hg higher tha that outside the artery The spongy tructure of the arterial wall has evolved for automatic sealing of punctures, and, in addition, the automatic sealing mechanism is temporarily strengthened by emergency filling of plasma-like substance into the extracellular space of the arterial wall by epinephrine this is the filling reaction of arterial walls

Part of the body reaction t trauma is the sensation of pain, which is accompanied, of course, by an outpouring of epinephrine Simultaneously there may be release of f tty materials At times the amount of fat released may be so great as t give rise t the clinical manifestation of fat embolism.

I an experimental study in which rabbit nd monkey were used demonstrated that fats of animal origin, such as lanolin, lard, rabbit fat, butyric acid palmitic acid, stearic acid, nd cholesterol, produced the generalized platelet sticking reaction and filling reaction of arterial lls when administered as single oral dose When epinephrine was also given the two reactions became much stronger and long lasting F ts of egetable orgn had no such effect.

I an additional investigation, the hindleg of the rabbit was traumatized 15 or 16 day after complete surgical denerv tion. This painless traumatization powerfully induced the platelet sticking reaction and the filling reaction, and al-o enhanced blood coagulability

I submit that Cannon emergency reaction should be expanded t include the filling reaction and the platelet sticking reaction, and I should al-o like t make the additional significant observ tion that fats of nimal origin imitat and also potentiate these reactions

W ha so far been unable t define the chemical nature of the mechanism which acts directly on the walls of the blood essels to produce these effects.

The filling reaction may well be key mechanism in therogenesis. The morphologic characteristics of the artery under these conditions stimulat *das f itsele fettfreie Ödem* of the German school, which has been proposed, since Virchow as the first stage in therogenesis. Moreover we[4] have found subst nces, synthesized by Professor Ishikawa, which are capable of preventing the filling reaction, as well therosclerosis in cholesterol-fed rabbits nd which ha striking effect in the prevention of experimental thrombosis

Elaboration of these studies ppears to be important in the search for the basic pathophysiologic mechanisms of thrombosis nd of therosclerosis.

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A proposed study for the prevention of pulmonary emboli

Pulmonary emboli kill thousands of people each year The following ideas are submitted proposal for diminishing the morbidity nd fatality rates due t this disorder

Upon returning t Los Angeles after training in the East, one of the uthors as greatly impressed by the relatively few cases of pulmonary emboli seen in Los Angeles Sa Francisco also ha relatively few cases of pulmonary infarctions. Other internists who hav previously worked in the East ha e had the same impression. Observations made on rounds at Harvard nd at New York nd London hospitals seemed to indicate that pulmonary emboli were common and often cause of death. The impression was that innumerable patients t the Massachusetts General Hospital had had their femoral eins ligated. There lso appeared to be more instances of emboli in winter tha in summer

Whether or not our impression is correct, the following studies ould be relevant on physiologic grounds. The first study although less feasible ma be mentioned Take t similar ards, each containing pproximately the same type of case Keep one ward relati ely warm, nd see that the patients ha plenty of blankets. Keep the other ard relatively cool so that the patients lower extremities might be little cold but thout subjecting the patient to discomfort The patients in the arm ward should ha an extra amount of fluid and salt. The incidence of pulmonary emboli in the relatively warm ward may be found t be ignifica tly reduced in comparison to the incidence the cooler ard. Meticulou care of room temper tures both temperatures kin temperatures (especiall of the lower extremities) must, of course, be observed

The second stud seems practical There might be some objections t arming the entire patient especially if he is in shock, or suffers from hypoxia or cardiac or respiratory disorders The more feasible project ould be t warm the lower extremities. This could be done ith an electric blanket ith controlled temperature, or leggings of electric blanket material thermostatically regulated to enhance the peripheral circulation only i.e., from foot t groin The measurement of the femoral ein arterial ox gen saturation ould be taken as an index of increased blood flow Arterialized blood has already been obtained in this manner i.e 9 per cent oxygen saturation of brachial ein blood. It ould not be desir ble t establish this maximum flow but an oxygen saturation of venous femoral ein blood approximately 10 per cent higher than the central level, i.e., 75 t 80 per cent.

The most feasible method of achieving enhanced local blood flow to the extremities is the thermostatically controlled leggings. If made in various sizes, they could be pulled on each extremity and kept there for 2 to 3 weeks before and 2 t 3 weeks after the operation, or ntil the patient becomes ambulatory

If the experiment could be set up in two or three hospitals, such as Veterans Hospitals in states in which cases of pulmonary emboli are frequent, it might be pos ible to obtain an answer at the end of year or so

This subject is manifestly more complicated than the single factor outlined. A tatistical survey of the incidence of this dreaded complication in the cooler cities compared with its incidence in the warmer cities ould also be relevant. Encouraging preliminary statistical information has already been obtained.

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Book reviews

ELECTROCARDIOGRAPHY. By Michael Bernreiter, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Kansas Medical School, and Chief of Electrocardiography, St. Mary's Hospital, Kansas City, Mo., Fellow of the American College of Cardiology and Fellow of the American College of Chest Physicians. Second edition. Philadelphia, 1963, J. B. Lippincott Company. 202 pages. Price $7.50.

The first edition of this book was reviewed in the AMERICAN HEART JOURNAL four years ago. Certain glaring deficiencies noted at that time still persist. For example, *relax* is given as a synonym for *repolarize*, and first-degree A-V block is unqualifiedly defined as a P-R interval above 0.20 second. The text remains inadequate in its treatment of both the theory and the practice of electrocardiography and cannot be recommended to those interested in either.

THE AFFERENT INNERVATION OF THE HEART. By A. Ya. Khabarova. Published in Russia in 1961 by the U.S.S.R. Academy of Sciences Press for the I. P. Pavlov Institute of Physiology in Moscow and Leningrad. Translated from the Russian by Basil Haigh, M.A., M.B., B.Chir. New York, 1963, Consultants Bureau. 175 pages. Price $12.50.

Dr. Khabarova's interesting book is as much a sociologic revelation as it is a scientific study. On the thirteenth page she announces uncharitably (and unscientifically) that all that can be found in the non-Russian literature on this subject is either a repetition of work done by Russian scientists or an insignificant addition. Because of this manifest chauvinism, it is amusing to note that she carefully acknowledges the use of two German, one Austrian, and two American makes of microscope. The citation of four times as many Russian as non-Russian references enhances the value of the bibliography for the non-Russian reader, but the omission of numerous classic studies from the Western world weakens the position of the author.

In essence this is an atlas of histologic observations on nerve endings in the heart. Forty human and 80 animal hearts were studied. No description of the gross anatomy of the nerves is provided. She divides the distribution of the nerve endings into those of endocardium, myocardium, and epicardium, but it is not clear what the basis for this arbitrary classification is. That the nerve endings studied were truly afferent rather than efferent endings is based on the premise that there is a difference in depth of staining, and on the result of denervating experiments. Virtually all the illustrations are drawings rather than photomicrographs, presumably because of the thick sections employed (nearly 100 micra). As the author indicates, such thick sections also made detailed examination of cells and fibers almost impossible, whereas thinner sections made it too difficult to identify entire nerve endings.

Orientation of the location of the sections is cursory except as to the depth in the myocardium. The value of the study would have been enhanced greatly with more attention to better orientation. One would like to know, for example, whether sections identified as being from the interatrial septum were close to the atrioventricular node or some distance from it. Almost no attention is given the pacemaker of the heart, one of the most richly innervated points in the heart.

This book is principally valuable for those interested in the histology of nerve endings in the heart. Other usefulness is greatly limited by the inadequate gross anatomic identification of the location of the sections studied.

FAT EMBOLISM. By Simon Sevitt, M.D., M.Sc., M.A., F.R.C.P.I., D.P.H., Consultant Pathologist, Birmingham Accident Hospital, formerly Consultant to the Medical Research Council Industrial Injuries and Burns Research Unit. Washington, D.C., 1963, Butterworth & Company. 233 pages. Price $11.95.

This little volume is said by the publishers to be the first comprehensive account of the subject in the English language. There are 13 chapters which discuss the etiology, origin, mode of action, and fate of fat emboli. The pathologic lesions are described and illustrated by numerous photomicrographs of good quality. The clinical features, diagnosis, treatment, and medicolegal aspects of fat embolism are presented.

The author is principally concerned with fat embolism after trauma to bone and soft tissue. The plasma chylomicrons are believed not to be important in fat embolism. Unfortunately, the author does not discuss fat embolism in patients with fatty livers, except in relation to trauma. The text is clearly written and the bibliography appears to be well chosen. There is considerable repetition in the several chapters, much of which is undoubtedly unavoidable.

Pulmonary fat embolism is believed to occur after most large fractures, but is thought to be of relatively little clinical significance, except as a source of systemic embolism. Coronary fat embolism is much less common than cerebral and renal fat embolism, and is believed to be seldom of clinical importance. For these reasons, this book is of only incidental interest to the cardiologist, but should prove to be a valuable reference to those who wish to read extensively on this subject.

INDICATIONS FOR OPEN HEART SURGERY: RISKS AND RESULTS. By Dryden P. Morse, M.D., Senior Attending Surgeon in Thoracic Surgery, Albert Einstein Medical Center, New York, Instructor in Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pa., Attending Surgeon,

Deborah Hospital, Browns Mills, N. J. Springfield, Ill., 1963, Charles C Thomas, Publisher. 213 pages. Price [redacted] 75.

The title to this little book is somewhat misleading. Chapters are systematically devoted to all the common and to many of the uncommon forms of congenital and acquired heart disease which can be treated by surgical means. Although emphasis is devoted mainly to the indications for and the risks and results of surgical treatment of each lesion, discussion is also given to such topics as incidence, pathology, symptoms, signs, x-ray films, angiocardiography, cardiac catheterizations, etc. The coverage of these latter topics is quite brief. Surgical treatment by closed-heart as well as open-heart procedures is included. Detailed surgical techniques were omitted purposely by the author.

This book should be of value to the internist, pediatrician, and general practitioner who has an interest in acquiring more knowledge in regard to the surgical aspects of cardiac disease. Of probable interest to the cardiologist is the appendix of the book, which provides a tabulation of the risks of operative treatment of specific lesions as reported from various cardiovascular centers around the world. Beyond these considerations, the book would appear to have little value. Coverage of the medical and diagnostic aspects of heart disease is too brief to be worth while.

Adequate references are provided for each section of the book. The indexing is good.

CARDIOMECHANICS. By Spyridon D. Moulopoulos, M.D., Associate Professor, School of Medicine, University of Athens, Athens, Greece; Research Fellow, Department of Artificial Organs, The Cleveland Clinic, Cleveland, Ohio. Springfield, Ill., 1963, Charles C Thomas, Publisher. 193 pages. Price $7.75.

This small book contains an outline of some aspects of the physiology of the heart as they appear to one interested in the design of artificial heart valves and blood pumps. Because of the wide range of topics mentioned, the treatment of each individual item is very scanty. Unfortunately, the full clarity and precision in the use of English which is vital in this type of work has not been completely achieved.

Announcements

COCHEMS COMPETITION. The University of Colorado School of Medicine announces the Cochems Competition, funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $2,500 will be awarded to the author of the best paper on the subject of *Involvement of the Venous System in Systemic Disease With Special Reference to Thrombophlebitis*. The competition is open to all physicians, and entries must be received, in triplicate, on or before *Aug. 15, 1963*. For income tax reasons, eligibility is limited only to those physicians who are subject to U. S. Income Tax regulations.

The Colorado National Bank of Denver, Trustees under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges, appointed by him, are Dr. Michael E. DeBakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine, Houston, and Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine, St. Louis.

Papers submitted in the competition may not be published until after the winner has been announced early in 1964. At that time, the winning paper and all others may be published at the discretion of individual authors. It should be noted, however, that those involved in conducting the competition will not assume any responsibility for submitting manuscripts for publication nor for any costs incident thereto. The winning paper, if published, must carry the designation, "Awarded the Jane Nugent Cochems Prize."

No entry blank or application is required. There are no restrictive rules in regard to the length or format of the manuscript, joint authorship, or inclusion of such materials as pictures, charts, figures, etc. The paper is not required to include results of original experimental work nor to be based on clinical personal experience. It is suggested, however, that all manuscripts be double spaced and submitted in a folder or cover. Papers will be judged on originality, content, clarity, and critique.

Inquiries in regard to the competition and all manuscripts should be submitted to Dr. John J. Conger, Acting Dean and Director of the University of Colorado Medical Center, 4200 East Ninth Avenue, Denver, Colorado 80220.

A postgraduate conference on RECENT ADVANCES IN CARDIOLOGY will be held at the Institute for Cardiopulmonary Diseases, Scripps Clinic and Research Foundation, Dec. 3-6, 1963. Principal guest speakers will be Dr. Irvine Page, Dr. Herman Hellerstein, and Dr. Larry Lamb.

Direct inquiries to Executive Secretary, Institute for Cardiopulmonary Diseases, Scripps Clinic and Research Foundation, 476 Prospect St., La Jolla, Calif.

Obituary

Paul Hamilton Wood, O.B.E., M.D., F.R.C.P.



Paul Hamilton Wood, 1907-1962.

The announcement of Paul Wood's death in July 1962, came as a profound shock to all who knew him personally and to many to whom his name and contributions to cardiology had been an inspiration.

His personality was so vital and his work so all-embracing that it seemed impossible to visualize the cardiological world without his dynamic presence and example.

Paul Hamilton Wood was born in India in 1907. He received his early education in England and later in Tasmania. Subsequently he studied medicine at Melbourne University, obtaining the degree of M.B., B.S. in 1931. Coming to England in 1933 he became a resident medical officer at the National Heart Hospital, where his intellect, ability and industry soon marked him for promotion. In 1935 he was appointed assistant to Professor F. R. (now Sir Francis) Fraser, the Director of the Department of Medicine of the newly formed British Postgraduate Medical School at Hammersmith Hospital, where important new advances in the study of the circulation were later made by McMichael and Sharpey Schafer. In 1937 he was appointed Physician to Out-patients at the National Heart Hospital and in 1941 Consultant Cardiologist to the Postgraduate Medical School. During the war, after a period in the Emergency Medical Service, when he made an outstanding contribution to the understanding of "Effort Syndrome," he served with distinction in the Royal Army Medical Corps, eventually becoming consultant physician to the Central Mediterranean Forces with the rank of Brigadier, being mentioned in dispatches and awarded the O.B.E. After the war he returned to the Postgraduate Medical School as Physician and Senior Lecturer and was soon appointed Dean and Director of the Institute of Cardiology at the National Heart Hospital.

Now began Wood's greatest and most productive years. With characteristic energy and vision he flung himself into the task of organizing the newly formed Institute, at the same time pushing forward the boundaries of cardiological knowledge with researches into valvular disease, congenital heart disease and pulmonary hypertension. As a result of his experiences he built up a mass of data on heart disease, his quick brain grasping at once the important features, constructing a detailed diagnostic discipline based on meticulous clinical observation supported by hemodynamic data. This work came to fruition in his St. Cyres Lecture on "Congenital Heart Disease" in 1950, in his Strickland Goodall Lecture on "An Appreciation of Mitral Stenosis" in 1954 and his Croonian Lectures on "The Eisenmenger Syndrome" in 1958, which are synthesized in his remarkable textbook. Wood's analysis of

the physiologic mechanisms responsible for signs and symptoms in heart disease was outstanding and has stood the test of time

It is not surprising that Paul Wood rapidly achieved international fame men came from all parts of the world to work with him and he traveled widely as a visiting professor and guest lecturer

Wood was many things to many people but certain facets of his character stood out with crystal clarity his intellectual power his piercing mind his ceaseless activity in the pursuit of knowledge and his interest in his patients and colleagues.

An evening spent with Wood was a stimulating experience for he never failed to arouse interest whatever the topic under discussion might be Provocative witty dogmatic and never boring he never appeared to be bored

With his passion for the truth he was intolerant of the false and shoddy He was no respecter of persons and did not suffer fools gladly so that on occasion he could be witheringly sarcastic Pomposity arrogance and self-satisfaction were anathema to him

He would listen carefully to any suggestion seriously made and discuss it thoroughly not hesitating to discard it if it failed to meet his exacting criteria but welcoming it if it satisfied these criteria even if it conflicted with his personal views and expressed opinions

He was prone to dogmatize in stressing a point of diagnosis or hemodynamics in order to stimulate argument and discussion for he did not appreciate too ready an acceptance of his views. So strong was his personality however that dogmatic statements were sometimes accepted at face value to an extent which he may never have intended

Beneath the somewhat curt exterior was a sympathetic personality an impish sense of humor and a capacity for compassion and understanding which was not always readily apparent to acquaintances.

It falls to very few to make as great a mark in medicine as Wood did in the field of cardiology Into a relatively short life he packed a wealth of experience and precept which exceeded many ordinary working lifetimes.

Those whom the gods love die young but Paul Wood as compensation for those who mourn him leaves behind a tradition in clinical cardiology a discipline of thought and of pragmatic reasoning in the physiology of disordered circulation and in diagnosis which will be his lasting memorial and an inspiration to all those devoted to the advancement of cardiological knowledge and to the care of the sick.

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Editorial

Management of the Stokes-Adams syndrome

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In the past decade we have witnessed major advances in the medical and surgical control of patients with A-V heart block and Stokes-Adams syndrome. Previously, therapy during the acute attack consisted primarily of intermittent parenteral injections of epinephrine and atropine. Drugs for maintenance therapy included ephedrine, atropine, and Paredrine. The introduction of sublingual isoproterenol in the early nineteen fifties was a step forward.[3] A more significant improvement in therapy of the Stokes-Adams syndrome came in the mid-nineteen-fifties with the use of dilute solutions of isoproterenol or epinephrine by continuous intravenous infusion.

Simultaneously with the improvement in drug therapy came the pioneer work of Zoll with external electronic stimulators. He opened a new field of electrical pacing of the heart during ventricular asystole or severe bradycardia. Stimulation by external pacemaker was soon supplemented by intracardiac stimulation through an endocardial catheter electrode placed in the right ventricle. Observations in experimentally induced heart block in dogs and surgically induced block in children with congenital heart disease soon showed that it was feasible to suture myocardial platinum electrodes to the ventricular myocardium and stimulate the ventricles by an external electrical pacemaker. Finally, in the past 3 years the use of transistors and miniaturization of the pacemaker unit have led to the present technique of subcutaneous implantation of the pacemaker and its connecting wires in the chest or abdominal wall. Although still beset by mechanical difficulties in 2 to 15 per cent of cases, the implantable pacemaker promises to become the device of choice for treating most patients.

At the present time various methods are available for treating the patient with unstable heart block during the acute stage of Stokes-Adams syndrome, and for maintaining therapy. The clinician must now decide how long to pursue medical therapy, when to use artificial pacing, and when to recommend surgical implantation of a pacemaker.

Drug therapy of Stokes-Adams syndrome

Isoproterenol and epinephrine. The patient with heart block, slow ventricular rate, and unstable rhythm is subject to "blackouts," syncopal episodes, convulsions, or sudden death due to ventricular asystole or fibrillation. This precarious

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situation constitutes a medical emergency that requires immediate resuscitative measures. The patient is given an initial parenteral injection of epinephrine (0.5 c.c. of 1:1000 solution) or isoproterenol (0.2 mg.). If he is seen during the actual episode of syncope or unconsciousness, the mechanical stimulation of a blow on the precordium or compression of the chest may revive ventricular contraction. If neither is successful, an intracardiac injection of epinephrine or isoproterenol (0.1 mg. in 10 c.c. of water) may produce mechanical followed by pharmacologic stimulation of the ventricles. The patient is then attached to an ECG monitor and an external electrical pacemaker, and a continuous intravenous infusion of isoproterenol or epinephrine is started promptly. The initial concentration is 2 mg. of isoproterenol or 2 c.c. of 1:1000 epinephrine per 1,000 c.c. of 5 per cent dextrose in water, and the rate of infusion is regulated to deliver a dose of 4 μg per minute (approximately 2 c.c. of solution per minute). If this concentration does not increase the ventricular rate to 40 to 50 per minute, it should be increased to 4 mg. of isoproterenol or 4 c.c. of epinephrine per 1,000 c.c. of solution. In severe cases, concentrations as high as 5 to 10 mg. of isoproterenol have been required.

Intravenous isoproterenol generally results in stimulation of an idioventricular pacemaker high in the A-V bundle or in one of the bundle branches. Often two distinct ventricular pacemakers may alternate. Continuous monitoring of the rhythm is necessary to detect signs of ventricular irritability (ectopic beats or tachycardia) and the rate of infusion must be slowed accordingly. No attempt should be made to increase the idioventricular rate above 45 to 50 per minute. Patients vary in their sensitivity to isoproterenol; some respond to concentrations as low as 2 mg. per 1,000 c.c. and others require up to 10 mg. per 1,000 c.c. Such intravenous infusions have been maintained for many hours or several days when necessary until stabilization of the cardiac rhythm occurs. The concentration and rate of infusion are then generally reduced until the patient can be weaned from intravenous medication. Intermittent intramuscular injections of isoproterenol (0.2 mg.) or epinephrine (0.5 c.c.) may then be continued, supplemented by sublingual isoproterenol (Isuprel) every 1 to 4 hours or oral Proternol (sustained action isoproterenol) every 4 to 6 hours.

Stokes-Adams syndrome is often precipitated by periods of ventricular tachycardia or fibrillation. In the patient with heart block this may be heralded by the appearance of bursts of ventricular ectopic beats. The tachycardia or fibrillation may alternate with periods of ventricular asystole. In such a case the use of isoproterenol or epinephrine is preferred to myocardial depressant agents such as quinidine and procaine amide. Careful infusion of isoproterenol or epinephrine by increasing the idioventricular rate and stabilizing a higher ventricular pacemaker may successfully prevent the recurrence of ventricular tachycardia and fibrillation. Quinidine and procaine amide will generally aggravate the myocardial depression responsible for the ventricular arrhythmia. Therefore, even when the mechanism of Stokes-Adams syndrome is proved to be ventricular tachycardia or fibrillation, the preferred method of therapy is the one used for ventricular asystole, except that lower concentrations and more careful titration of intravenous dosage and monitoring of cardiac rhythm are necessary. In addition, countershock with the external electrical AC defibrillator instead of the external electrical pacemaker is applied during any recurrence of syncope or when there is prolonged ventricular tachycardia or fibrillation.

Corticosteroid. In some cases of recurrent ventricular asystole or marked bradycardia, corticosteroid therapy may effectively increase the ventricular rate, prevent asystole, and stabilize A-V conduction. In acute situations the rapid administration of a corticosteroid agent may be lifesaving. Its effect becomes manifest within several hours. This applies particularly to A-V block associated with acute myocardial infarction or myocarditis, in which case the anti-inflammatory action of the corticosteroid reduces the edema and cellular reaction within and around the A-V conduction system. Such an effect is readily understandable, but it is difficult to explain the occasional complete or

partial abolition of chronic A-V block or bundle branch block in the absence of clinical signs of infarction or carditis.[11] The latter effect is probably caused by a direct enhancement of A-V conduction, possibly resulting from depletion of intracellular potassium in the conduction tissues.

Dosage of the corticosteroid must be relatively high, beginning with 60 to 80 mg. daily of prednisone or an equivalent dosage of methylprednisone (40 to 50 mg.) or triamcinolone (30 to 40 mg.) or dexamethasone (9 to 12 mg.) and after several days progressively reducing the daily dose to half the initial dose. This dosage should be maintained until the maximum effect has been obtained (resumption of normal sinus rhythm or a stable ventricular rhythm). In acute emergencies, therapy can be instituted by an immediate intravenous injection of hydrocortisone, 100 to 200 mg., followed by oral dosage as outlined above. Corticosteroid therapy should be given a trial in all cases when there is no contraindication to its use (gastrointestinal ulcerations, etc.).

Quinidine and procaine amide. The danger of administering quinidine or procaine amide to patients with Stokes-Adams syndrome has been repeatedly emphasized. These agents are myocardial depressants which further impair A-V conduction. Even when ventricular tachycardia or fibrillation is present, these drugs may aggravate or perpetuate ventricular irritability by their depressant effects on the myocardium and should not be used routinely. Occasionally, a beneficial antiarrhythmic effect is obtained when other measures have failed. The better alternative, as already mentioned, is the cautious intravenous infusion of isoproterenol in weak concentrations, in an attempt to increase the rate of the higher ventricular pacemakers and block the lower ectopic ventricular center responsible for the tachycardia. Potassium salts also have a depressant effect on A-V conduction and should not be used in block, even when it is produced by digitalis toxicity.

Digitalis. This drug, too, must be used with great caution in cases of Stokes-Adams syndrome. By its vagal and direct myocardial actions, it depresses A-V conduction. This occurs not only in partial block, but also in advanced or complete A-V block, in which case it may affect the idioventricular center below the A-V node, causing further slowing of the ventricular rate and predisposing to ventricular asystole and Stokes-Adams attacks. I have observed several patients with partial or complete A-V block who developed intractable Stokes-Adams syndrome after they were digitalized with a relatively small dosage because of signs of congestive failure. Digitalis therapy in such cases is safe only after insertion of an intracardiac catheter electrode or implantation of an electrical pacemaker, which ensures control of ventricular rate after digitalis has been administered. Under these circumstances, digitalis may abolish heart failure by improving ventricular contraction and increasing stroke output.

Maintenance drug therapy

Isoproterenol is the drug of choice for maintenance therapy after parenteral therapy has been discontinued.[18] The sublingual tablet (Isuprel) is absorbed rapidly, and within a few minutes a high peak of action is attained which is dissipated in a relatively short time. It is useful, therefore, when the patient has premonitory symptoms of standstill or slowing of the rate, such as lightheadedness or transient blackout. For continuous maintenance therapy, it should be given *at frequent intervals (every 2 to 4 hours) in doses of 5 to 15 mg.*, depending on its effect on ventricular rate and whether *or not* it produces palpitation or angina.

Oral sustained-action tablets of isoproterenol (Proternol), now available for clinical use, are recommended for long-term maintenance therapy in chronic A-V block.[19] This drug has been most effective when an unstable cardiac mechanism persists after therapy for acute Stokes-Adams syndrome. Its beneficial effect may be manifested by restoration of normal sinus rhythm or lesser degrees of heart block or by maintenance of a faster idioventricular rate. Long-term experience (up to 3 years) has indicated that the incidence of recurrent ventricular asystole and Stokes-Adams attacks can be significantly reduced. Side effects, such as palpitation, ventricular irritability, or

tachycardia are much less frequent than with sublingual administration since absorption is slower. The peak effect on ventricular rate, however, may be maintained for 2 to 4 hours. The usual dosage is one tablet (30 mg.) every 4 to 6 hours around the clock; in some cases a dosage of 60 mg. every 6 hours has been effective.

Interim pacing of heart by bipolar endocardial electrode

Electrical pacing of the heart by a bipolar catheter electrode inserted into the outflow tract of the right ventricle through a jugular or antebrachial vein represents another major advance in the therapy of Stokes-Adams syndrome.[12] It can be accomplished rapidly and with ease under local anesthesia. Once the bipolar electrode has been properly positioned in the outflow tract of the right ventricle and connected to the electrical pacemaker, a relatively small stimulus (2 to 5 volts) will capture control of ventricular excitation and maintain a regular ventricular rate (50 to 70 per minute).

The method is applicable for patients with either recurrent ventricular asystole or fibrillation or with slow ventricular rates. It gives the clinician complete control of ventricular pacing without the discomfort to the patient and the other disadvantages of external electrical stimulation. It results in improved cardiac output and stable blood pressure and the alleviation of heart failure and coronary insufficiency. For patients who respond poorly to isoproterenol or epinephrine or who show undue sensitivity to these drugs, prompt insertion of the catheter electrode is indicated. When there is lack of significant response to drug therapy, recurrence of symptoms, instability of ventricular rhythm, or evidence of congestive heart failure in the presence of a slow ventricular rate, then drug therapy is supplemented with the endocardial bipolar electrode.

After insertion of the catheter, intravenous infusion of isoproterenol or epinephrine can be discontinued. If heart failure is not abolished after the ventricular rate is increased, digitalis can be given in therapeutic dosage without fear of depressing A-V conduction. Diuretic therapy can also be administered in the usual manner. At present, this method is used routinely in the preoperative preparation of all our patients who require surgical implantation of a pacemaker.

Indications for surgical implantation of a cardiac pacemaker

Although modern drugs have considerably improved the medical management of the patient with A-V block and Stokes-Adams syndrome, the long-term results of therapy and the prognosis are still disappointing. The incidence of recurrent Stokes-Adams syndrome and death within the first 6 to 12 month follow-up period remains high. For this reason, we now advise surgical implantation of an electrical pacemaker in all patients in whom there has been a major Stokes-Adams attack or a history of recurrent attacks. It is also recommended for patients with slow ventricular rates below 40 per minute despite adequate drug therapy, particularly when faintness or recurrent blackout occurs because of inadequate cerebral blood flow. Patients with A-V block and congestive heart failure are also candidates for operation since their low cardiac output can be improved only by increasing the ventricular rate. The dangers of digitalis therapy in such patients have been previously emphasized, and intensive dietary and diuretic therapy alone may fail to restore adequate cardiac output.

With improved surgical techniques and preoperative preparation, most patients can tolerate operation successfully with a relatively low mortality.[4] Even patients with previous myocardial infarction and extensive ventricular damage and fibrosis have been operated on successfully. Great caution must be exercised to exclude the patient with recent myocardial infarction, since the operative risk is high and sudden death may occur. Furthermore, A-V block during acute myocardial infarction is often transitory and will revert to normal rhythm spontaneously or with adequate drug therapy. If the block becomes permanent, then surgery can be considered when the myocardial infarction has healed (generally not before 2 to 3 months). If Stokes-Adams attacks recur during the acute or healing stage of infarction, or if severe brady-

cardia or unstable ventricular rhythm persists, interim pacing of the ventricles with the intracardiac bipolar catheter should be maintained until A V conduction improves spontaneously or until the patient is considered ready for surgical implantation of a pacemaker

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Clinical communications

Pathology of heart diseases of undetermined etiology which occur in Cali, Colombia

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Reports from different parts of the world have drawn attention to the occurrence of heart diseases which cannot be classified in any of the usual well-defined groups of congenital, inflammatory, atherosclerotic, and pulmonary etiology. This group of heart diseases constitutes a problem of considerable magnitude in Africa and has aroused a growing awareness that the epidemiologic pattern of heart diseases in the tropics does not conform to the usual pattern seen in the temperate zones of North America and Europe, where atherosclerosis is the leading cause of death.

In Central and South America there are reports of heart diseases of undetermined etiology which constitute an important medical problem. These are usually considered to be sequelae of Chagas' disease in the areas of Brazil and Argentina[illegible] in which Chagas' disease is endemic, and to be chronic myocarditis with a possible background of hypersensitivity in Venezuela[illegible] and Guatemala. Reports from Colombia have referred to cases of isolated myocarditis[illegible] and idiopathic cardiac hypertrophy.[illegible] The latter term was applied to a group of 11 cases which were studied in this laboratory because of inadequate knowledge of their etiology and pathogenesis.

The lack of adequate criteria for determining the etiology of these diseases has forced investigators to group them together. Davies[illegible] recently pointed out that there are almost certainly different pathologic entities within the same group. Accurate pathologic descriptions of the different types of lesions are needed in order to define the disease entities as a basis for further epidemiologic studies. The purpose of this report is to present our examination of a group of heart diseases of undetermined etiology and to point out some of the pathologic differences.

Material

From 1954 to 1961 a total of 930 adult autopsies were performed by the Department of Pathology of the School of Medicine of the Universidad del Valle. Th

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autopsy rate has fluctuated from 64 to 76 per cent in this period.

These autopsies were reviewed and classified. After cases of congenital heart disease were excluded, a total of 233 cases were found in which cardiovascular disease was considered to be the cause of death. In this material, 28 cases of heart disease of undetermined etiology were found, and these cases form the series reported in this paper. Complete autopsy was performed in all of them, and the study was further completed with a thorough microscopic examination, including more than 20 sections taken from different areas of the heart, stained with hematoxylin and eosin, Mallory trichrome, reticulum, elastic, and Van Gieson stains.

Results

The relative frequency of cardiovascular disease in this autopsy population is shown in Table I. It is to be noted that hypertension is responsible for the majority of cardiovascular deaths. Heart disease of undetermined etiology ranks as the second most frequent cause of death; the number of cases is not significantly different from the figure for cases of rheumatic heart disease but is definitely higher than the corresponding figures for myocardial infarction and cor pulmonale.

Since this is a hospital series, we have tried to compare this material with a study that better represents the mortality in our community. Preliminary data of a special mortality study being carried out by our medical school in collaboration with the Pan American Health Organization were analyzed.[8] From May 1 to July 31, 1962, a total of 460 deaths occurred in Cali in the age group 15-74 years. All the information available on these patients was reviewed by a medical team, and a final diagnosis was reached on the basis of the available evidence. In 116 the primary cause of death was a cardiovascular disease distributed as follows: hypertensive disease, 52; cardiopathies of undetermined origin, 40; myocardial infarction, 10; rheumatic heart disease, 5; syphilitic and saccular aneurysms, 3; dissecting aneurysms, 3; others, 3. These figures confirm the frequency of hypertensive disease as observed in the autopsy series; they also show that there is a considerable number of deaths due to heart disease which cannot be diagnosed specifically on clinical grounds alone. At autopsy, however, a specific etiological diagnosis can be made in the majority of these cases.

Clinical findings. A summary of the principal clinical and laboratory findings in the series of cases is presented in Table II. There were 18 female and 10 male patients. Age limits ranged from 20 to 80 years; the average ages were 54.2 for the males and 48.5 for the females. Distribution of the cases according to race was as follows: mestizo, 13; Negro, 7; white, 7; and mulatto, 1. This racial distribution probably reflects only the extreme mixed characteristic of the population of Cali.

The most frequent chief complaint was dyspnea, which suggests left heart failure as the usual initial phase of the disease. Peripheral edema frequently supervened within a short period, which indicates the development of congestive heart failure.

Table I. Relative frequency of noncongenital cardiopathies in 930 necropsies in adult, 1954-1961

Diagnosis		Number of cases	Per cent
Hypertension		77	33.03
Essential	50		
Glomerulonephritis	14		
Pyelonephritis	13		
Undetermined etiology		28	12.01
Rheumatic		26	11.15
Myocardial infarct		20	8.58
Cor pulmonale		20	8.58
Bacterial endocarditis		11	4.71
Syphilitic aortitis		10	4.29
Aortic aneurysms		7	3.00
Myocarditis		5	2.14
Amyloid heart		4	1.71
Pericarditis		4	1.71
Senile heart		4	1.71
Calcific aortic stenosis		4	1.71
Hyperthyroidism		2	0.85
Malnutrition*		2	0.85
Aortitis (Takayasu)		1	0.42
No diagnosis†		8	3.47
Total		233	

*Includes one case of severe fatty metamorphosis secondary to nutritional anemia, and one case of clinical beriberi.
†Material insufficient for accurate diagnosis.

Table II. Clinical findings in 28 cases of cardiopathies of undetermined etiology

Case number	*Age (yr.)*	*Sex*	*Race*	*Chief complaint*	*Duration (mo.)*	*Blood pressure (mm. Hg)*
1	48	F	Mestizo	Dyspnea	27	140/110
2	65	F	Mestizo	Dyspnea	2	130/ 80
3	50	F	Mulatt	Dyspnea	3	145/100
4	37	F	Mestizo	Edema	4	90/ 70
5	38	F	White	Cough	7	100/ 70
6	46	M	White	Cough, dyspnea	48	120/ 80
7	43	F	Negro	Gangrene of right leg	6	100/ 60
8.	60	M	Negro		6	100/ 60
9	20	F	Mestizo	Dyspnea	3	145/ 85
10	40	F	Mestizo	Dyspnea, edema	3	120/ 80
11	60	M	Mestizo	Abdominal pain	2	110/ 70
12.	48	F	Mestizo	Dyspnea	4	160 80
13	[illegible]	M	Negro	Dyspnea	Several	115/ 80
14	40	F	Negro	Dyspnea, edema	3	—
15	67	M	White	Dyspnea, edema	5	120/ 95
16	51	M	Negro	Dyspnea	24	125/ [illegible]
17	48	F	Mestizo	Dyspnea, edema	3	130/ 80
18	80	F	White	Dyspnea, edema	12	140/ 80
19	70	F	Negro	Bloody diarrhea	12	120/ 90
20	33	M	White	Dyspnea	13	110/ 90
21	58	F	Mestizo	Dyspnea, abdominal pain	8	110/ 85
22.	32	F	Mestizo	Cough, fever	5	100/ 80
23	55	F	White	Dyspnea, edema	7	150/ 70
24	42	M	Mestizo	Hemiplegia	3	—
25	55	M	Mestizo	Dyspnea	7	140, 90
26	28	F	Negro	Dyspnea	11	110/ 70
27	66	M	White	Dyspnea, abdominal pain	6	Shock
28.	73	F	Mestizo	Dyspnea, abdominal pain	9	110/ 70

Gangrene of the right lower extremity, intestinal infarction, and hemiplegia were prominent clinical findings in 3 patients at the time of admission to the hospital.

Blood pressures were within normal limits, except in 2 patients in whom the diastolic pressures were slightly elevated.

Arrhythmias, mainly extrasystoles, were found in 19 patients. A gallop rhythm was noted in 7 patients. In 18 patients a Grade 1-2/4 apical soft systolic murmur was heard, and in another patient a diastolic rumble was heard associated with a systolic murmur. No murmurs were discerned in 9 patients, but in these the heart sounds were of low intensity.

Electrocardiographic studies were performed in 20 patients. The most frequent deviations included abnormal P waves, low voltage in the limb leads, and nonspecific ST-T changes which involved especially the limb leads, V and V (Fig. 1). These findings were compatible with pericarditis or diffuse myocardial damage. In one case, QS complexes were observed from Lead V to Lead V and interpreted as anteroseptal infarction. In several cases frequent extrasystoles were recorded, 2 of which cases showed bigeminal rhythm. Two cases showed varying degrees of A-V block suggestive of digitalis toxicity. Atrial fibrillation and left bundle branch block were also among the electrocardiographic abnormalities.

Rhythm	*Gallop*	*Murmur*	*ECG study*	*Chest x-ray examination*
Sinus	−	Apical systolic	Diffuse myocardial damage	Cardiomegaly
Sinus with extrasystoles	−	Apical systolic	Not done	Cardiomegaly
Atrial fibrillation	−	Diffuse systolic	Not done	Not done
Sinus	+	Apical systolic	Left bundle branch block	Cardiomegaly
Atrial fibrillation	−	Apical systolic	Not done	Not done
Sinus	+	None	Left bundle branch block	Cardiomegaly
Atrial fibrillation	−	Apical systolic	Not done	Not done
Sinus with extrasystoles	+	Apical systolic	Diffuse myocardial damage	Cardiomegaly
Sinus	+	None	Diffuse myocardial damage, complete A V block	Normal heart size
Atrial fibrillation	−	None	Diffuse myocardial damage, atrial fibrillation	Not done
Atrial fibrillation	−	None	Left bundle branch block, atrial fibrillation	Cardiomegaly
Sinus with extrasystoles	−	Apical systolic	Diffuse myocardial damage	Cardiomegaly
Sinus	−	None	Not done	Not done
Sinus with extrasystoles	−	Apical systolic	Diffuse myocardial damage	Not done
Sinus with extrasystoles	−	None	Not done	Not done
Atrial fibrillation	−	Apical systolic	Diffuse myocardial damage	Cardiomegaly
Sinus with extrasystoles	−	Apical systolic	Diffuse myocardial damage	Not done
Atrial fibrillation	−	Apical systolic	Diffuse myocardial damage, atrial fibrillation	Cardiomegaly
Sinus with extrasystoles	+	Apical systolic	LV systolic overloading	Cardiomegaly
Sinus with extrasystoles	−	Apical systolic and diastolic	"Compatible with anteroseptal infarct	Cardiomegaly
Sinus with extrasystoles	−	Apical systolic	Not done	Cardiomegaly
Sinus with extrasystoles	−	Apical systolic	Left ventricular hypertrophy left atrial hypertrophy	Normal heart size
Sinus	−	Apical systolic	Not done	Cardiomegaly
Sinus	−	None	Not done	Not done
Atrial fibrillation	−	None	Diffuse myocardial damage, atrial fibrillation	Cardiomegaly
Sinus	+	Apical systolic	Left ventricular and left atrial hypertrophy	Cardiomegaly
Sinus	+	None	Left bundle branch block	Cardiomegaly
Sinus with extrasystoles	−	Apical systolic	Left bundle branch block	Cardiomegaly

Radiologic study of the thorax was performed in 20 patients. A global enlargement of the heart was usually associated with pulmonary congestion in 18 of the patients. Bilateral pleural effusion was also a frequent finding. In only 2 patients was the heart considered to be of normal size.

No other significant laboratory findings were observed except for sickle cell trait in 1 patient. Thromboembolic phenomena occurred in 14 patients and will be mentioned in the pathologic discussion.

The clinical course from the onset of symptoms to death ranged from 2 to 48 months. 15 patients died within 6 months. The usual therapeutic regimen for congestive heart failure had very little or no influence on the course of the disease, since full myocardial compensation was never achieved. Digitalis toxicity was easily induced.

Pathologic examination. Gross and microscopic findings in these cases are summarized in Table III. A careful study of these hearts revealed several differences that led us to reclassify them into three pathologic types. *Type I* shows as the main feature the presence of focal progressive myocardial lysis, usually but not constantly associated with bilateral hypertrophy of the heart, mural thrombi, and fibrosis of the endocardium with slight or no inflammatory reaction. *Type II* is characterized mainly by the presence of

Table III. Pathologic findings in 28 cases of cardiopathies of undetermined etiology

Case number	Type	Heart weight (Gm.)	Mural thrombosis	Endocardial fibrosis	Focal myocardial lysis	Leukocytic infiltrate of pericardium	Emboli	Atheroma of coronaries
1	I	750	LV	LV	+	−	Lungs	+
2	I	400	LV	LV	+	+	Lungs, kidney	−
3	I	480	LV	LV	+	+	—	−
4	I	561	LV	LV	+	−	Kidney, spleen	−
5	I	500	RV, RA	—	+	+	Lung, kidney	−
6	I	700	—	LV	+	−	—	+
7	I	400	LV	LV	+	−	Lung, spleen, kidney, right leg	−
8	I	327	LV, RA	LV, RV, RA	+	+	Lung, brain	+
9	I	400	LV, RV, RA	LV, RV	+	−	Lung, kidney	−
10	I	400	All chambers	LV	+	−	Kidney	−
11	I	510	LV, both atria	LV, RA	+	−	Lungs, intestine	+
12	I	600		Both ventricles, RA	+	+	—	−
13	I	600	LV	—	+	+	—	−
14	I	380	Both ventricles, RA	All chambers	+	+	Lungs	−
15	I	450	Both atria	LV	+	−	Lungs, spleen, ileal	+
16	I	800	—	LV	+	−	—	−
17	I	350	LV, RA	Both ventricles, LA	+	+	Lungs, spleen, intestines	+
18	I	350	LV	LV	+	−	—	−
19	II	300	LV	LV	−	−	Lung, intestines	−
20	II	380	—	Both ventricles	−	−	—	−
21	II	450	—	Both ventricles	−	−	Lungs, kidney	+
22	II	320	LV	Both ventricles	−	−	—	−
23	III	375	LV	—	−	−	—	−
24	III	200	LV	—	−	−	Brain	−
25	III	500	RA	—	−	−	Lungs	−
26	III	400	LV	—	−	−	Lungs, spleen, kidney	−
27	III	600	RV	—	−	−	Lungs	−
28	III	350	LV	—	−	−	—	−

LV, Left ventricle; RV, Right ventricle; RA, Right atrium; LA, Left atrium.

endocardial fibrosis associated with moderate bilateral hypertrophy without myocardial lysis. *Type III* is a heterogeneous group of cases having certain characteristics in common, principally mural thrombosis associated with hypertrophy and dilatation of the heart, which are placed together only for purposes of discussion. A detailed presentation of each one of these groups follows.

TYPE I. FOCAL PROGRESSIVE MYOCARDIAL LYSIS. We have classified into this group 18 cases in which focal loss of myocardial fibers was the constant finding. Three lesions were recognized which may represent stages of the disease: (1) lesions of lysis of the sarcoplasm, which seemed to be the earliest change since, occasionally, nuclei and/or paranuclear pigment could be identified lying free in apparently empty spaces surrounded by sarcolemma and the normal myocardial reticulum (Figs. 2 and 3); (2) lesions in which there was complete disappearance of the nuclei and sarcoplasm with only the sarcolemma remaining (Fig. 4); (3) lesions in which myocardial fibrosis was present (Fig. 5). These lesions were all devoid of significant leukocytic or macrophage infiltration, and all three lesions were often seen in the

same heart section. Occasionally small foci of mononuclear leukocytes were seen in the myocardium away from the areas of fiber lysis.

In the less extensively involved hearts, lesions were present which involved only the septum and the apical regions and occasionally involved the trabeculae carneae and the papillary muscles (Fig 6). The two or three fibers immediately adjacent to the endocardium were always spared. In the more extensively involved hearts lesions were also present in the other layers of the myocardium.

Fibrous thickening of the endocardium was observed in 16 cases. When present it usually involved the apical endocardium of the left ventricle and occasionally other heart chambers. Fibrosis was also frequently observed surrounding the papillary muscles (Fig 7).

Mural thrombosis was seen in 15 cases, usually covering areas of endocardial fibrosis. The apex of the left ventricle was constantly the site of lesions, mainly myocardial atrophy and endocardial fibrosis and thrombosis (Figs 8 and 9).

Coronary arterial lesions were not conspicuous. Small atheromatous plaques were noted in 6 cases. Hemorrhage, stenosis, thrombosis, and calcification were not present. All the hearts of these patients were hypertrophic and dilated; the average weight was 497 grams. The degree of hypertrophy was usually related to the duration of symptoms.

TYPE II. ENDOCARDIAL FIBROSIS. In 4 cases, endocardial fibrosis was the prominent finding and was not accompanied by lysis or necrosis of the myocardium. Fibrous tissue with thick collagen bands replaced the endocardium and extended to the adjacent myocardium in the form of fine projections (Figs. 10 and 11). As seen in Table III, fibrosis was invariably present in the left ventricle. In this chamber fibrous changes were very extensive, covering the apex and the inflow tract completely and, to a minor degree, the outflow tract. Papillary muscles were also surrounded by fibrous tissue. Fibrosis was also encountered in the right ventricle in 3 cases. This was less extensive and occurred in patches in scattered areas. Thrombosis was present in the left ventricle in 2 cases. In one instance it covered the apex and in the other it was represented by a flat layer of fibrinous material which covered most of the surface of the ventricle (Fig 12). Only in this type were valvular lesions found, in 2 instances of which the proliferation of fibrous tissue fused the papillary muscles, the chordae tendineae, and part of the valvular cusp to the mural endocardium, producing obliteration of the normal angle formed by the heart wall and the valvular apparatus (Figs. 13 and 14). This change was seen in the anterior leaflet of the mitral valve in one case and in the anterior leaflet of the tricuspid valve in the other. There was a moderate cardiac hypertrophy; the average weight of the heart was 362 grams.

TYPE III. MURAL THROMBOSIS. These cases illustrate the findings of heart disease which have as the only postmortem manifestations those of cardiac hypertrophy, dilatation, and thrombosis.

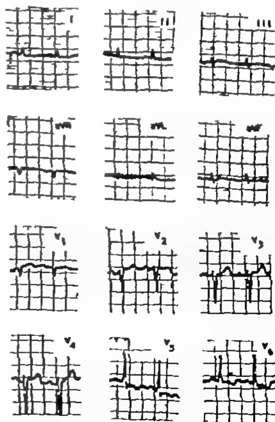


Fig. 1. Typical electrocardiogram showing low voltage in the limb leads and ST-T changes, especially in Leads V and V6.

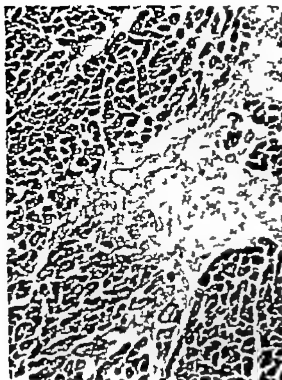


Fig. 2. Area of myocytolysis showing loss of sarcoplasm and preservation of nuclei and sarcolemma. (Hematoxylin and eosin, ×118.)



Fig. 3. Area of myocytolysis with loss of sarcoplasm and preservation of nuclei and sarcolemma. (Hematoxylin and eosin, ×460.)

In 2 cases there was marked leukocytic infiltration of the thrombus and the adjacent myocardium, thereby suggesting an infectious agent as the cause of the thrombosis. In one of these cases the thrombosis was also present in the right carotid artery and led to cerebral infarct.

In one example there was thrombosis of the portal and innominate veins, as well as thrombosis of the superior vena cava. These changes were apparently due to a sickle cell crisis, since the thrombi represented a large accumulation of crescent-shaped erythrocytes, and an AS hemoglobin pattern was noted by electrophoresis.

In the other 3 cases of this group there was cardiac hypertrophy and dilatation. Mural thrombosis in different chambers was found: in the left ventricle in one case, left atrium in a second case, and right atrium in the third case. The endocardium and the myocardium were otherwise not remarkable. The patients died of heart failure, and no other disease was found clinically or at autopsy.

Discussion

This material shows that cardiac diseases of undetermined etiology are an important source of illness and mortality in our area. It also shows that not all cardiac syndromes of obscure origin can be considered to represent a single disease. They do have in common similar clinical manifestations and certain pathologic findings, such as cardiac hypertrophy and dilatation and mural thrombosis. All of the evidence at hand indicates that these syndromes are not produced by hypertension, rheumatic fever, coronary atherosclerosis, or syphilitic disease. Although we are far from having a clear idea of their etiologies, a discussion of the several factors that might be related to them is indicated.

Type I. This peculiar type of myocardial lysis is the most frequent of the lesions in our series. An attempt to compare our observations with those of other reports may be helpful in the analysis of possible etiological factors.

Recent reports from other South American countries have called attention to the

observation that in areas in which Chagas infection is endemic a chronic form of heart disease is frequently found which may be a late manifestation of previous infection with *Trypanosoma cruzi* [12,1] The pathologic pattern described in such cases closely resembles that of our material As in our cases the changes included dilatation and hypertrophy focal fibrosis of the endocardium and the myocardium and mural thrombosis, especially frequent in the apex of the left ventricle and in the right atrium with a peculiar atrophy of the myocardium at the apex. Our material however did not show the prominent leukocytic infiltrate reported in the foci of recent myocardial lesions.

The parasite was never found in our material. It is possible as pointed out by Köberle, that the final stages of Chagas cardiopathy are not directly related to the presence of *Trypanosoma cruzi* and the inflammatory reaction but are secondary to the heart lesions induced by the parasite many years previously However



Fig. 5 Low-power view of the left ventricle showing focal fibrosis of the myocardium. Subendocardial fibers are preserved. Endocardial thickening is minimal and there is marked capillary dilatation.



Fig 4 Low-power view of papillary muscle showing myocytolysis (center) with preservation of the peripheral fibers and absence of important endocardial fibrosis.

to our knowledge lysis of the myocardial fibers in the absence of inflammatory reaction as seen in our cases, has not been reported in Chagas disease.

Several observations of acute Chagas disease have been reported from one area of Colombia where the disease is endemic [16,20] Vectors naturally infected with *Trypanosoma cruzi* have been found in several areas of Colombia.[22] In the region of Cali, however *Trypanosoma cruzi* has not been isolated from either human beings or animals. Furthermore cases similar to ours have been reported from different parts of the world where Chagas disease is not known to exist.

The clinical picture described for chronic Chagas heart disease is similar to that observed in our cases, except for the fact that the finding of right bundle branch block which is given a high diagnostic value in areas in which the disease is endemic,[14] was not found in any of our cases

There are marked similarities of the lesions under consideration and those described by Gillanders, Becker and Hig



Fig 6 Low-power view showing area of myocardial lysis involving the inner portion of the myocardium and the trabeculae carneae

gunson and associates from South Africa.[1,27] They have in common cardiac hypertrophy and dilatation, endocardial fibrosis, mural thrombosis more remarkable in the left ventricle and right atrium, fibrosis of the inner layers of the myocardium, and areas of myocardial degeneration described as hydropic degeneration or moth-eaten fibers. These authors also stress the absence of important leukocytic infiltrate. Although the myocardial lesions are not thoroughly illustrated in their papers, it seems that there are no substantial differences between the South African cardiopathies and those of our material. For these African cardiopathies several etiological theories have been offered. They were first thought to represent some form of nutritional deficiency.[34] It has not been possible to present definite evidence for this theory. No specific clinical nutritional deficiency was found in our cases. Becker[35] considered an etiology of hyper

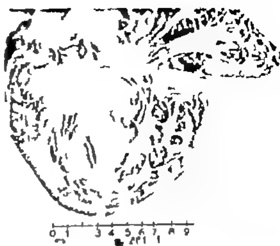


Fig 7 Gross appearance of the heart showing area of endocardial thickening of the left ventricle



Fig 8 Photograph showing fibrosis of the apex of the left ventricle and atrophy of the muscle at this level.

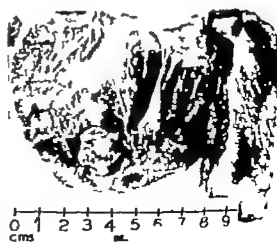


Fig 9 Photograph showing thrombosis of the apex of the left ventricle



Fig. *10* Photograph showing diffuse thickening and fibrosis of the endocardium of the left ventricle

sensitivity for these lesions, on the basis of the finding of mucoid degeneration arteritis and fibrinoid changes of the collagen We observed fibrinoid degeneration and verrucous changes of arterioles in one case. These however seemed to be the exception rather than the rule, and therefore, we are not inclined to consider these lesions as representative of the basic etiological factors of these cardiopathies. Higginson[17] has also considered the possibility that the common factor is a weakness of the myocardium which could be due to different agents. This would lead to thrombosis and fibrosis as secondary complications, which would then be responsible for the myocardial necrosis. We have failed to find a direct relationship between the sites of thrombosis and the sites of myocardial lysis, and we do not believe that the myocardial lysis is secondary to thrombosis or fibrosis of the endocardium We agree in considering the endocardial changes as secondary to myocardial disease and set forth the theory that the myocardial lysis is the morphologic representation of the primary myocardial damage

A theory of infectious process should be considered Myocarditis of obscure origin has been described in Bogota Venezuela and Guatemala.[28] The lack of prominent leukocytic infiltrate in our cases does not favor a theory of infectious process for these lesions. In fact as shown in Table I we separated the cases of myocarditis from this group Whether the lesions represent sequelae of a previous myocarditis be it bacterial viral or parasitic cannot be proved at this stage

The type of myocardial lysis with preservation of the stroma and absence of inflammation has been described in detail by Schlesinger and Reiner[29] They found it at the periphery of myocardial infarcts and as foci of miliary necrosis. In 5 of their cases this lesion appeared in patients



Fig. *11* Low-power view of the section of the same heart stained with Mallory trichrome Dark areas correspond to fibrosis of the endocardium covering the wall and trabeculae carneae



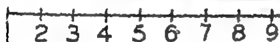


Fig. 12. Photograph of the left ventricle showing flat layer of thrombus which covers most of the endocardial surface. Only small area of the septum is not covered by the thrombus.

with heart failure which at autopsy did not have any of the common types of cardiac pathologic pattern. These would be similar to our findings, except that mural thrombosis and endocardial fibrosis were not described in their cases.

It is possible that the cause of these cardiopathies might be found in factors which produce lysis of the myocardial fibers. Most authors favor an anoxic theory for the production of these changes.[23] It has been supposed that in cases of endocardial fibrosis the transendocardial nutrition of the myocardium would be curtailed and would result in the death of myocardial fibers. This may be possible but not always true because we have observed cases of marked and extensive thickening of the endocardium in the absence of myocardial lysis (see Type II below). We have also observed myocardial lysis not accompanied by endocardial thickening. If anoxia were to explain myocardial damage in these cases, true necrosis accompanied by disappearance of sarcolemma and myocardial reticulum would be expected as well as loss of fibers in sharply defined areas; these characteristics were absent in our cases.

Whorton's finding[24] of heart diseases due to the presence of abnormal myoglobin representing an inborn error of metabolism might open new possibilities for investigation in this group of obscure cardiopathies. Myocardial lysis has been produced under several experimental conditions.[23] This has led Schlesinger and Reiner to believe that myocardial lysis is the final morphologic manifestation of different etiological agents. The frequency of this lesion in our material suggests that some special factors—toxic, nutritional, or other—are consistently present within our ecological medium.



Fig. 13. Photograph of the anterior leaflet of the tricuspid valve showing fusion of the papillary muscle, chordae tendineae, and part of the valve cusp to the mural endocardium.



Fig. 14. Low-power view of the microscopic section of the same heart. Fibrous tissue fills up the space between the valvular apparatus, chordae tendineae, and the heart wall.

Type II. This type of endocardial fibrosis has some similarity to the lesion described by Davies in Uganda, except for the involvement of the outflow tract to some extent in our patients, and the presence of embolic phenomena in 2 of our patients. The absence of myocardial lesions leads us to believe that this disease is related to some obscure endocardial injury. Endocardial fibrosis is known to develop in localized zones of turbulence such as occurs in cases of valvular insufficiency. However, the extensive distribution of the fibrosis in our cases, the absence of elastosis, and the lack of marked dilatation of the heart do not point to a pure mechanical factor as the cause of these changes. Some type of chemical injury to the endocardium would be more in accord with the lesions observed.

Type III. Some of the cases described in the Type III group may actually represent instances of mural endocarditis of bacterial origin. However, we have no evidence to confirm this etiology. Furthermore, the striking similarity of the clinical and gross pathologic features of these cases to those of the cases grouped under Types I and II forced us to consider them as part of the group of heart diseases of undetermined etiology.

Summary

Heart disease of unknown etiology is a common cause of death in Cali. Clinical characteristics are described in 28 cases; pathologic patterns found at autopsy allowed the definition of two distinct pathologic types and a third type which consisted of miscellaneous findings grouped together for purposes of discussion. Type I is characterized by the presence of focal progressive myocardial lysis with or without mural thrombosis and endocardial fibrosis. Type II is characterized by endocardial fibrosis with or without mural thrombosis and no myocardial lysis. Type III is a heterogeneous group characterized by mural thrombosis, hypertrophy, and dilatation.

The similarities of our cases to, and differences from, other cases reported are discussed, and a brief review of the etiological agents considered is made.

Addendum

After this manuscript was completed our attention was called to an article in which diffuse myocytolysis is described in proved cases of Chagas' disease in Brazil.

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Intracardiac phonocardiography of the left heart by transseptal left atrial puncture

Technique and preliminary results

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During recent years intracardiac phonocardiography has provided much information about the relationship of the various events of the cardiac cycle.[1-4] It also has been of great value in the diagnosis of acquired and congenital heart disease. In most instances, however, the recording of acoustic phenomena from within the heart is limited to the right side of the heart, since during routine cardiac catheterization a microphone catheter cannot be introduced into the left side of the heart in the presence of a sealed foramen ovale. Lewis and co-workers have recorded intracardiac phonocardiograms of the left atrium and left ventricle in a few cases in the open chest at the time of operation for mitral stenosis. Retrograde catheterization of the aorta and the left ventricle with a microphone catheter has also been unsuccessful in most instances. The development of a microphone catheter small enough to be used in catheterization of the left side of the heart was not yet possible. Another method of left heart intracardiac phonocardiography was described by Luisada and Liu. These authors used a column of saline or glucose solution within the catheter as the carrier of sound waves during transthoracic puncture of the left atrium or left ventricle. With this method the electrical output of the strain gauge is differentiated, amplified, and filtered and is recorded by a phonocardiograph. Catheterization of the coronary sinus with a microphone catheter has also been used in order to record the murmurs originating at the mitral valve. In most instances, this technique is unsatisfactory for the recording of the sound phenomena of the left side of the heart.

The introduction of transseptal left heart catheterization by Ross and Cope[8] has been a major step forward in achieving safe access to the left side of the heart. The original method has been modified by several authors,[9-11] and transseptal heart catheterization is now used in this laboratory for routine left heart catheterization, left ventriculography, and left-sided intracardiac phonocardiography.

Materials and methods

Transseptal left heart catheterization has been performed in 200 patients with acquired and congenital heart disease as well as in some normal subjects. All patients but one were in the pediatric age

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group. The youngest patient was 1 year old at the time of the investigation. In the first 20 cases the method originally described by Ross[7] was employed. Later we used a *radiopaque* polyethylene catheter (Ödman-Ledin, yellow) as a guide for the 17-gauge Ross needle. The tip of this catheter was tapered and its distal end was shaped with a curvature in order to facilitate its passage into the left ventricle. During the introduction of the catheter into the right atrium via the saphenous vein, the curvature of the catheter was straightened by a stylet. After puncture of the left atrium, the polyethylene catheter was pushed over the puncture needle and advanced further into the left atrium and left ventricle. This modification has been described in detail by Brockenbrough and Braunwald.[8] Teflon catheters with a curvature at the tapered tip are now available* and may be used instead of the Ödman-Ledin catheters.[13]

The inside diameter of the yellow Ödman-Ledin catheter is 1.15 mm. and does not permit the introduction of a microphone catheter. The Teflon catheter of the Brockenbrough set has an inside diameter of 1.70 mm. and its tip is tapered to about 1.0 mm. The tip of the smallest microphone catheter,† however, is approximately 1.5 mm. in diameter and cannot be passed through these catheters. In order to make the introduction of a microphone catheter possible, we used a special Ödman-Ledin catheter with an inside diameter of 1.9 mm. and an outer diameter of 2.8 mm. This catheter is prepared in the same manner as mentioned above and is used for transseptal left atrial puncture with a 17-gauge Ross needle. After puncture of the left atrium the catheter is pushed over the needle and advanced into the left ventricle. The needle is then withdrawn. When blood has been obtained for determination of oxygen, and after the recording of pressures, the microphone catheter is introduced into the catheter and advanced until its tip has passed the tip of the guiding catheter and until it is positioned within the left ventricle. The transseptal left heart catheter is then withdrawn

*U.S. Catheter and Instrument Corporation, Glens Falls, N. Y.
†Lumenics Electronic Laboratories, 121 North Seventh St., Philadelphia, Pa.

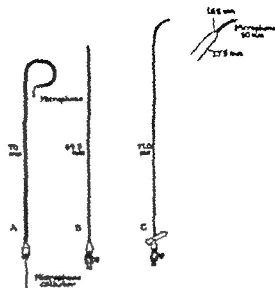


Fig. 1. Set of instruments used for transseptal left heart intracardiac phonocardiography.

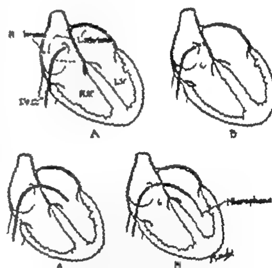


Fig. 2. Schematic drawing of the technique of intracardiac phonocardiography of the left side of the heart.

completely and an intracardiac phonocardiogram of the left ventricle can be recorded. It is advisable to withdraw the Ödman-Ledin catheter, since its presence within the left heart may disturb the recording of the intracardiac phonocardiogram. The sound catheter is then withdrawn from the left ventricle into the left atrium for the recording of the left atrial phonocardiogram. Finally, it is completely

withdrawn through the puncture hole in the interatrial septum.

With this technique intracardiac phonocardiograms of the left side of the heart have been recorded in 25 patients. A set of Teflon catheters and transseptal needles which permits the introduction of a microphone catheter into the left side of the heart is now commercially available (Fig 1) The Teflon catheter has an inside diameter of 1 75 mm and is tapered at its tip to an inside diameter of 1 65 mm It is 70 cm. long and its distal end is shaped with a curvature in order to facilitate its passage into the left ventricle Curvatures are available in three different sizes (diameter 2.0 2.5 3.0 cm.) A flare at the proximal end of the catheter permits its connection to a commercially available adapter To facilitate the introduction of the catheter into the right atrium an 18-gauge stylet is introduced into the catheter in order to straighten the curvature at its tip. The stylet is 69.5 cm. long The transseptal puncture needle employed for puncture of the interatrial septum is 71 cm long and is similar to the needle described by Ross Fig 2 is a schematic drawing of the technique and Fig 3 shows a roentgenogram of a patient with the microphone catheter in the left ventricle. The transseptal catheter has already been withdrawn into the left atrium

It should be pointed out that the intracardiac phonocardiography catheters of the American Electronic Laboratories with an acoustic pickup only are supposed to be of approximately No 5 French in size The microphone at the tip of the catheter and the catheter itself should have a diameter of only 1 50 mm. Some of these catheters however may have a greater diameter and their introduction into the transseptal catheter may be difficult or impossible Only microphone catheters with a diameter of 1 50 mm. can be used

Results

Fig 4 shows a recording from within the left atrium of a normal person There are two distinct components of the first heart sound The first is due to closure of the mitral valve and coincides with the same vibrations recorded within the left ventricle The second vibration is the aortic component of the first sound and probably is transmitted from the aorta into the left atrium through direct contact of these two structures. The second heart sound is also transmitted into the left atrium through the wall of the aorta and the left atrium It follows the mitral opening sound before the vibrations due to rapid filling of the left ventricle are recorded within the left ventricle The mitral opening sound is followed by vibrations due to atrial contraction Fig 5 shows phonocardiograms recorded within the left atrium and left ventricle of a patient with mitral stenosis. No murmur is recorded in the left atrium. Within the left ventricle the opening sound of the mitral valve is followed by a distinct presystolic murmur This is in agreement with Lewis who pointed out that the murmur of mitral stenosis can be recorded only in the left ventricl and not in the left atrium.



Fig 3 Microphone catheter in the left ventricle of 6½-year-old patient, introduced through the special transseptal catheter The guiding catheter has already been withdrawn int the left trium.

*U. S. Catheter and Instrument Corporation, Glens Falls, N. Y.

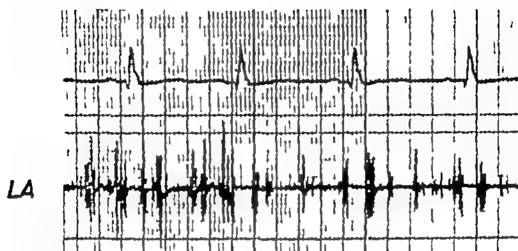
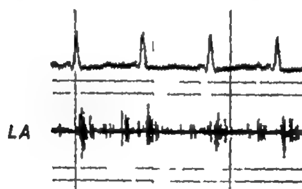


Fig. 4. I t ac rd phc liogr m recorded i the left tri m of normal subject. I per speed is 50 mm. per second. H time lines re 0.5 second. In the first t complexes the i ter l between the begin ing of the t omponent of the first he rt sound i 0.05 second; i the last two omplexes it i 0.10 second.



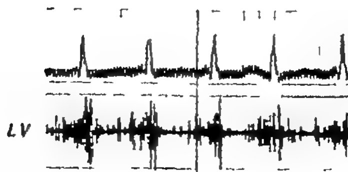


Fig. 5. I t ac rdiac phono d gr ms re ded in the left trium nd left ent icle of p tient th mitr l tenosis. I per speed is 50 mm. per second. Hea y time lines re 0.5 second.

An intracardiac phonocardiogram recorded in the left ventricle of a normal subject is shown in Fig. 6. The pressure tracing has been superimposed. There are two components of the first heart sound. The first component in all our tracings is taller than the second one. It coincides with the closure of the mitral valve. The second and smaller component seems to coincide with the opening of the aortic valve. This is in contrast to the findings of Luisada and coworkers,[18] who found that the first component of the first sound within the left ventricle is smaller than the second one. The second heart sound within the left ventricle is represented by a somewhat

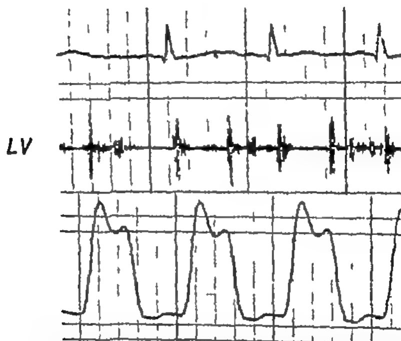


Fig. 6. Intracardiac phonocardiogram recorded in the left ventricle of a normal person. The pressure tracing has been superimposed. Paper speed is 50 mm. per second. Heavy time lines are 0.5 second. The left ventricular pressure curve has been superimposed according to the electrocardiogram originally recorded in both tracings.

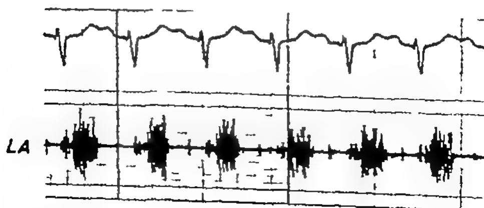


Fig. 7. Intracardiac phonocardiograms recorded in the left atrium of a patient with pure pulmonary stenosis. Paper speed is 50 mm. per second. Heavy time lines are 0.5 second.

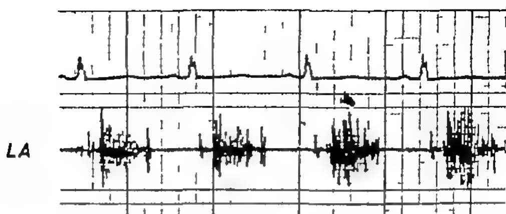


Fig. 8. Intracardiac phonocardiogram recorded in the left atrium of a patient with supravalvular aortic stenosis. Paper speed is 50 mm. per second. Heavy time lines are 0.5 second.

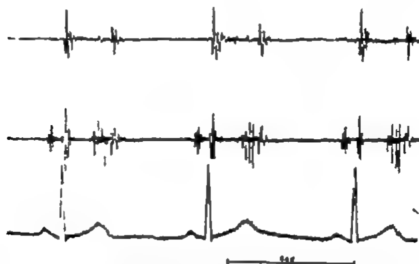


Fig. 9. Intracardiac phonocardiogram recorded in the left atrium of a patient with combined mitral stenosis and insufficiency and aortic insufficiency. *Top*: Extracardiac phono. *Center*: Intracardiac phono from left atrium. *Bottom*: ECG. There is the systolic murmur of mitral regurgitation in the left atrium.

higher vibration than the first sound and is single. It is due to the closure of the aortic valve. The third and the fourth heart sounds are also well recorded.

Lewis[6] has reported on the transmission of murmurs from the pulmonary valve into the left atrium. Fig. 7 shows the phonocardiogram recorded in the left atrium of a patient who had pure pulmonary stenosis with an intact atrial septum. The first component of the first heart sound which originates at the mitral valve upon its closure, is clearly separated from the beginning of the systolic murmur. Fig. 8 is the recording made within the left atrium of a patient with supravalvular aortic stenosis. The murmur is transmitted through the wall of the aorta and left atrium. The vibrations of the first component of the first heart sound are separated from the beginning of the aortic systolic murmur which begins only after the opening of the aortic valve.

Figs. 9 and 10 are the intracardiac phonocardiograms recorded in a patient with combined mitral stenosis and insufficiency

and aortic insufficiency. The systolic murmur of mitral insufficiency can be recorded in the left atrium. There is no presystolic murmur of mitral stenosis in the left atrium. In the left ventricle the systolic murmur of mitral regurgitation and the diastolic murmur of aortic insufficiency, as well as the presystolic murmur of mitral stenosis, can be recorded.

Discussion

Intracardiac phonocardiography of the right side of the heart with a microphone catheter is now widely used during cardiac catheterization in patients with congenital heart disease. The recording of heart sounds from within the left side of the heart, however, has been limited to a small number of patients. The introduction of transseptal left heart catheterization has provided an easy and safe route to the left side of the heart, and left heart catheterization should be carried out routinely at the time of right heart catheterization. If a catheter with an inside diameter of 1.75 mm. is used for transseptal left heart catheterization, a microphone catheter can be introduced through this catheter into the left side of the heart. The addition of left heart intracardiac phonocardiography to complete right and left heart catheterization will be of value in the diagnosis of congenital and acquired heart disease. More information about the transmission of cardiac sounds and murmurs from and into the left side of the heart may be obtained by this method.

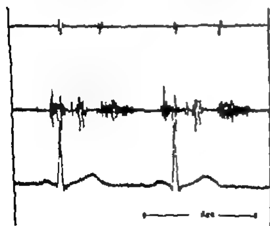


Fig. 10. Intracardiac phonocardiogram recorded in the left ventricle of a patient with combined mitral stenosis and insufficiency and aortic insufficiency. *Top*, Extracardiac phono. *Center*, Intracardiac phono. *Bottom*, ECG. The systolic murmur of mitral regurgitation can be recorded in the left ventricle. There is also the diastolic murmur of aortic insufficiency and the presystolic murmur of mitral stenosis.

The tracings shown in Figs. 4 and 6 confirm observations made by Luisada[13] on the pattern of cardiac sounds. There is, however, a constant difference in the relative size of the first and second components of the first heart sound in the left ventricle in our tracings as compared to the findings of Luisada and co-workers.[13] Luisada has pointed out that the first component of the first sound in the left ventricle is smaller than the second component. In our tracings the first component has always been larger than the second component. Since the first component is due to closure of the mitral valve, and sounds and murmurs are transmitted in the direction of blood flow, it is probable that the closing sound of the mitral valve is louder in the left ventricle than is the second component of the first sound, which is due to opening of the aortic valve.

The transmission of the murmur of pulmonary stenosis into the left atrium, as shown in Fig. 7, has already been reported by Lewis and co-workers. These authors also reported on a flow murmur originating at the pulmonary valve in normal individuals. The question has been raised whether this normal murmur may be produced by the presence of the catheter in the pulmonary valve. The authors pointed out that the normal pulmonary artery murmur could also be recorded in the left atrium when there was no catheter in the pulmonary artery. In the present series we were able to record only the murmur of pulmonary stenosis in the left atrium or pulmonary vein, and in no instance was a normal pulmonary artery murmur transmitted into the left atrium.

The intracardiac phonocardiogram of the left atrium and left ventricle may be of importance in the differentiation of mitral and aortic valve disease. Liu and associates have pointed out that the murmur of mitral insufficiency can only be recorded in the left atrium and not in the left ventricle. However, Lewis and co-

workers believe that the murmur of mitral insufficiency is present in the left ventricle. As shown in Fig. 10 there is a systolic murmur in the left ventricle due to mitral regurgitation. Further observations are necessary on this question.

Summary

A new technique for intracardiac phonocardiography of the left side of the heart is described. If a catheter with an inside diameter of 1.5 mm. is used for transseptal left heart catheterization, a microphone catheter with a diameter of 1.50 mm. can be introduced into the left side of the heart through the transseptal catheter. Preliminary results in 25 patients are presented.

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The relationship between digitalis and A V nodal tachycardia with block

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Paroxysmal atrial tachycardia with block has been considered to be the most frequent supraventricular arrhythmia produced by digitalis overdosage However there is increasing evidence that nonparoxysmal nodal tachycardia might be at least as frequent as the former [1] A relatively unknown digitalis-induced toxic rhythm is nodal tachycardia associated with conduction disturbances, which, as a rule appears in a nonparoxysmal form Its incidence was considered to be low but this is due to the fact that the different varieties of this arrhythmia have been grouped under various headings. In addition it is obvious that unless long strips of tracing are taken and the observer is aware of this arrhythmia irregular nodal activity due to nodal tachycardia with exit block might not be diagnosed correctly especially in the presence of atrial fibrillation [4]

Even though digitalis is not the only cause of the rapid A V nodal activity it is undoubtedly by far the most common etiological agent In view of the theoretical importance of the recognition of a fairly recently described arrhythmia, we considered important an evaluation of the relationship between A V nodal tachycardia with block and digitalis. The effects produced by short-acting digitalis preparations were also studied

Material and methods

The tracings of 36 subjects which showed nonparoxysmal nodal tachycardia with block were studied In 25 instances the correct electrocardiographic diagnosis was made within a 9 month period during which time a total of 17 650 records was obtained in our institution They were screened by at least three observers who had been alerted to the basic features of the arrhythmia The tracings were obtained from our files in five instances and have been included in other publications[6-12] by one of the co-authors (A C) Nonparoxysmal nodal tachycardia was diagnosed whenever the ectopic rate was over 80 per minute, exceeding 200 beats per minute in only one patient, who had congenital heart disease. The different varieties, depending on the existing conduction disturbance were classified according to Pick, Langendorf and Katz as can be seen in Tables I II and III The ages of the patients ranged from 10 to 78 years arteriosclerotic heart disease (ASHD) was present in 26 cases. The amount of digitalis given to each individual was obtained from the corresponding clinical chart The scale used to evaluate this amount was the following +++ for those cases in which the arrhythmia appeared after initial digitalization ++ for those cases in which the disturbance in rhythm was seen to

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Table I. Data on the various types of A-V nodal tachycardias with block: Atrial fibrillation

Case number	Etiology	QRS duration (sec.)	Nodal rate	Block	Scale of digitalization	Type of digitalis	Other arrhythmias
2	CHD (postsurgical)	0.08	225	2:1, 3:2 (EB)	+++	—	
3	ASHD	0.12 (CLBBB)	98-104	2:1, 3:2 (EB)	+++	DO	
5	ASHD	0.09	93	2:1 (EB)	+++	DO	
13	ASHD	0.12 (CLBBB)	100	2:1, 3:2 (EB)	+++	DO	Double A-V tachycardia*; A-V tachycardia with antegrade A-V block
18	ASHD	0.06	91	2:1 (EB)	++	DL DO	
19	ASHD	0.06	150	2:1, 3:2 (EB)	0	—	
20	ASHD	0.12	150	2:1, 4:1 (EB)	+	DI	
23	RHD	0.08	200	2:1 (EB)	+++	AF	
24	ASHD	0.10	86	2:1, 4:1 (EB)	+++ +++	DL DO	
33	CHD (postsurgical)	0.07	124	2:1 (EB)	0	—	
34	RHD	0.08	140	2:1, 4:1 (EB)	+++	DO	
35	RHD	0.07	124	2:1 (EB)	+++	DL	

*The arrhythmias appeared on two separate occasions.

CHD, Congenital heart disease. ASHD, Arteriosclerotic heart disease. RHD, Rheumatic heart disease. CLBBB, Complete left bundle branch block. EB, Exit block. DF, Digoxin. DL, Digitalis leaf. DI, Digitoxin. AF, Acetylstrophanthidin.

Table II. Data on the various types of A-V nodal tachycardias with block: Retrograde conduction

Case number	Etiology	QRS duration (sec.)	Nodal rate	Block (degree)	Scale of digitalization	Type of digitalis	Other arrhythmias
1	CHD (postsurgical)	0.09	140	Second (R)	+++	—	
4	CHD (postsurgical)	0.08	150	Second (R)	+++	—	
10	ASHD	0.07	75	Second (R)	++	DI	
11	ASHD	0.08	143	First (A)	+++	DO	
12	ASHD	0.08	100	Second (A)	+++	DI	
14	ASHD	0.07	120	First (A)	++	DL DI	Ventricular bigeminy
16.	ASHD	0.10	87	First (A)	+++	DL	
21	ASHD	0.08	80	First (A)	+++	DO	
22.	ASHD	0.07	87	First (A)	++	DO (probable)	
27	ASHD	0.07	107	First (A)	++	DO	
28*	ASHD	0.07	130-170	First (A) Second (A)	++	DO AF	A-V tachycardia
30	ASHD	0.06	158	First (A)	++	DO AF	A-V tachycardia
31	CHD (postsurgical)	0.13 (CRBBB)	175	Second (A)	0	—	
32.	CHD (postsurgical)	0.12 (CRBBB)	160	Second (A)	0	—	
36.	ASHD	0.08	111	First (A)	+++	DO	

CHD, Congenital heart disease. ASHD, Arteriosclerotic heart disease. CRBBB, Complete right bundle branch block. R, Retrograde (V-A) block. A, Antegrade (A-V) block. DI, Digitoxin. DO, Digoxin. DL, Digitalis leaf. AF, Acetylstrophanthidin.

occur after the maintenance dose had been *increased* or a switch to other digitalis preparations had been made and + for the cases in which paroxysmal nodal tachycardia with block was seen during maintenance dosage. The digitalizing and maintenance doses were the usual for the corresponding preparations.[21]

Results

Of the 36 cases studied there were 5 in which the corresponding records showed certain characteristics which were considered to be of interest in respect to the morphology of nonparoxysmal tachycardia with block and (or) its relationship to digitalis. The corresponding electrocardiograms are presented in Figs. 1 through 5 and are fully described in the respective legends. Tables I II and III show the basic data. The rate of the A V pacemaker ranged from 80 to 225 per minute, with an average of 109 It was 200 or more only twice (Case 2 with congenital heart disease and Case 23 with rheumatic heart disease) Total QRS duration ranged from 0 06 to 0 14 second but 7 patients had definite bundle branch block by standard electrocardiographic criteria. In instances of atrial fibrillation it was observed that 2 1 exit block was present twelve times 3.2 four times and 4 1 three times On two occasions it was seen that carotid sinus pressure produced an increase in the degree of exit block. In patients with retrograde conduction second-degree ventriculo-auricular block occurred three times, and atrioventricular block twelve times. (Nine of the latter cases showed first degree and 3 presented second-degree A V block.) In the double nodal tachycardias, it was found that the atrial rate (due to the activity of the higher pacemaker) was regular in all instances. However the R R intervals were irregular in 5 patients. The irregularity was ascribed to complete ventricular captures four times to incomplete captures twice (concealed conduction[23] that is, depression of impulse formation of the lower pacemaker

Table III Data on the various types of A V nodal tachycardias with block Double and bidirectional

Case number	Etiology	QRS duration (sec)	Upper pacemaker rate	Lower pacemaker rate	Scale of digitalization	Type of digitalis	Other rhythmias	Ventricular capture
Double nodal tachycardias								
6.	ASHD	0 06	88	103	+++	DO	—	*
7	CHD	0 14 (CRBBB)	92	111	++	DO	A V T	Complete Incomplete†
8.	ASHD	0 12 (CLBBB)	80	94	+++	DL AE	A-V T	Complet
9	ASHD	0 13 (CLBBB)	90	130	++	DO	A V T	No
13	ASHD	0 09	82	100	++	DI	—	Complet
17	ASHD	0 08	125	150	+++	DO	—	*
25.[14]	ASHD	0 06	80	100	+++	ADO	A-V T	Incomplete†
36.	ASHD	0 08	145	68‡	+++	DO	A V with A	Complet
Bidirectional nodal tachycardias								
26	ASHD	0 06–0 08	103 (sinus)	167	+++	DG	PAT	
28.	ASHD§	0 08	100 (sinus)	150	+++	DG		
					+++	DL		

*Irregularity of the R R cycles caused by the Wenckebach phenomenon of A-V conduction from the lower pacemaker to the ventricles.
†Considered as the depressant effects of supraventricular impulses on the automatic function of the lower pacemaker
‡Rate of lower pacemaker under 80.
§The arrhythmia appeared on two separate occasions.
ASHD, Arteriosclerotic heart disease. *CHD* Congenital heart disease. *CRBBB* and *CLBBB*, Complete right and left bundle branch block, respectively DO, Digoxin. DL, Digitalis leaf. *AE*, Acetyl strophanthidin. *DI* Digitoxin. *ADO* Acetyl digoxin. *DG* Digalen. *A V T* A-V tachycardia. *A*, Antegrade (A-V) block. *PAT* Paroxysmal atrial tachycardia with block.

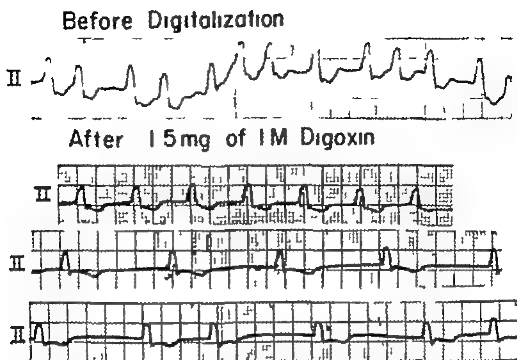


Fig. 1. Case 3. The appe ance of A-V nodal tachy rdia with 2:1 and 3:2 exit block after digitalization in patient ith atrial fibrillation nd left bundle branch block. *The upper strip* was obt ined from 68-year-old patient k ASHD at the moment of admission. The patient who was congestive heart failure and had received no digitalis recentl had been known to have atrial fibrillation nd left bundle branch block for s. The ecord show idened (0.12 sec.) and bizarre nevenly spaced QRS complexes, and is consistent ith the diagnosis of trial fibrillation with a fast ventricular response nd left bundle branch block. *The second strip* taken after digitalization and mass e diuresis shows regula ventricular rh thm with a rate of 104 per min. R-R interval 0.57 sec.) (nonparoxysmal tach cardia). The ectopic pacemaker was considered to be in the A-V node because the bundle branch block as present previously and the QRS complexes ere similar t those which occurred when A-V conduction wa present. The sequence of events (regularization of previously irregula entricula rtion during trial fibrillation fter digitalization) is strongly suggesti e of digitalis intoxication. Atrial fibrillation as still present nd def nitely seen in the right chest leads (*not shown*). This consideration is importa t because trial flutter with 2:1 A-V block might conceiv bl be present (even though no F wa es ere seen in Lead II). I *the third str p* the te of the nodal pacemaker is 52 per min. (R-R interval 1.14 sec.) which is half of that present in the second strip. Therefore 2:1 exit block from the nodal pacemaker to the entricles ca be implied as the mechanism hich causes the slowing of the ntricular rate. I *the fourth strip* an irregular entricular action can be observed. Careful nalysis reveals that this irregularity was not caused by the unequal conduction of impulses originating in the atria. F idently the first R-R interval measures the same those in the third trip thus ndicating that the same nodal tachycardia exist now with 2:1 exit block. Thereafter the second and third R-R intervals measure 72 nd 112 sec ndoubtedly shorter and longer respectively than the basic one. Such irregularity ca be explained by the sudden onset of 3:2 exit block, the rate of the pacemaker now being 98 per min. The y le length can be obtained by adding 72 nd 112 nd di iding by 3 (61.3 = rat of 98 per min.)

by the higher ectopic center) and to the Wenckebach type of A-V conduction once (Fig. 2).

In 11 patients, other types of arrhythmia immediately preceded or followed the one under study. These were also considered to be drug induced. In Cases 24 and 28 A-V tachycardia with block occurred on two separate occasions each time with a different digitalis preparation.

Digitalis had been given to the patients prior to the appearance of the arrhythmia in 29 out of 30 of the clinical cases. Tables I-III show that in the majority of the cases the arrhythmia appeared after initial digitalization especially after mobilization of fluids.

Comments

The study of 36 cases of nodal tachycardia which showed various types of con disorders is useful for evaluating

the relationship of the arrhythmia to digitalis therapy. The implication was that digitalis definitely induced the arrhythmia in 29 patients (81 per cent). According to the scale employed, toxicity was considered to be present in 27 patients. However, we believe that evidence has been presented which shows that digitalis excess is not necessarily the only cause of nodal tachycardia with block. Evidently there were 2 cases (Fig. 3) in which the arrhythmia appeared during the treatment of spontaneous nodal tachycardia coexisting with atrial fibrillation. The spontaneity of the latter was suggested by the large amounts of acetyl strophanthidin employed for were the original rhythm due to toxicity other deleterious effects would have been expected with small doses.[15] In addition it was noted that after oral digitalization of the patients the electrocardiographic picture was that of a slow atrial fibrillation with irregular ventricular response. This finding indicated that the 2:1 exit block of nodal tachycardia was an intermediate stage during transition from ectopic to basic rhythm, which disappeared with further digitalization.

Full digitalizing doses were given to one half of the patients in whom the disturbance of rhythm was present after operation. However, in the other half the tachycardia appeared spontaneously and was abolished by drug therapy. This small series seems to indicate what has been stressed by other authors, namely, that nodal rhythms which appear during these periods seem to be related more to surgical trauma per se than to digitalis. The first three sets of tracings were obtained at a time when all of the patients with congenital heart disease were digitalized routinely preoperatively; the other three were taken at a time when none of them was digitalized preoperatively. It is well known that ectopic impulse formation in the A-V node seems to be more frequent in those operations which involve the correction of septal defects.[4-]

Nearly all of the nonsurgical patients reported on in this communication had advanced heart disease and were over 60 years of age. The disorder of rhythm appeared with different preparations, but, since digoxin is the one most frequently used in our hospital, it is understandable



Fig. 2. Case 6. Double nodal tachycardias with irregular R-R cycles in which the irregularity is caused by the Wenckebach phenomenon of A-V conduction from the lower pacemaker to the ventricles. The record was obtained from a 61-year-old patient with ASHD after initial digitalization. The P waves, appearing at regular intervals, were negative in Lead II as well as Leads III and aVF (not shown). The R-R cycle measures 0.68 sec., therefore indicating nodal tachycardia (rate 88 per min.). However, all R-R intervals are unequal, but the irregularity cannot be ascribed to the effect of the upper pacemaker (producing complete or incomplete captures), as can be seen in other published examples of double tachycardias. On the contrary, careful analysis reveals that the R-R pattern follows a particular form, characteristic of the Wenckebach phenomenon: (1) There are groups of three or four beats separated by pauses; (2) within the longer runs of faster beats the cycle shortens progressively; hence (3) the last R-R interval before the intermission is always shorter than the first R-R interval after the intermission, and (4) the intermissions measure less than if the consecutive short R-R intervals are added. This pattern, as can be seen in the diagram, indicates that there is a second (rapid) A-V pacemaker discharging at a rate of 103 per min. (faster than the higher center), showing alternately 4:3 and 5:4 A-V conduction toward the ventricles. In addition, there is complete impedance of transmission toward the atria (as well as from the higher pacemaker to the ventricles). Whether this impedance to conduction is due to normal or prolonged refractoriness (true block) is not definitely known. The lower pacemaker was considered to be located above the bifurcation, as can be gathered from the normal (0.06 sec.) QRS duration.

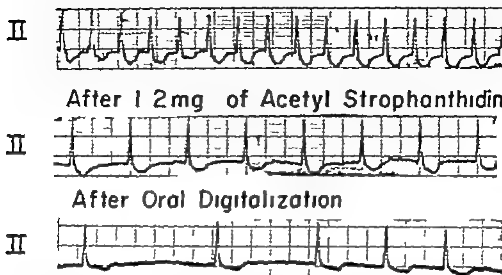


Fig. 3. Case 23. A-V nodal tachycardia with 2:1 exit block appearing after acetyl strophanthidin. These tracings were obtained from a 44-year-old woman with rheumatic heart disease and chronic fibrillation. The upper strip was taken while she was on maintenance doses of digoxin after she suddenly developed palpitations accompanying mild congestive heart failure. The R-R intervals correspond to a rate of 200 per min., and the QRS complexes measure 0.06 sec. No P waves were seen in the conventional twelve-lead ECG. The rate of 200 (ruling out atrial flutter with 2:1 A-V conduction) and the absent P waves suggested nodal tachycardia. The main problem at this point was whether the rhythm was "spontaneous" or drug induced. Therefore, a digitalis tolerance test was performed. After 1.2 mg. of acetyl strophanthidin, the ventricular rate dropped to 100, exactly one half of the previous rate, but still regular. Consequently, a 2:1 exit block from the nodal pacemaker to the ventricles was assumed. Atrial fibrillation is now clearly present, evidence of which are the tiny undulations in Lead II. Two hours later the patient received a full oral digitalizing dose. The ECG taken the following day revealed atrial fibrillation with a slow and irregular ventricular response. The irregularity could not be ascribed to varying degrees of exit block as in Fig. 1.

that the majority of instances of overdosage occurred with this drug (Tables I-III). We observed that the arrhythmia was most frequently seen after initial digitalization, a finding which might be related in part to the fact that tracings were taken more frequently during this stage even in the absence of clinical signs of toxicity.

It has been suggested that nonparoxysmal nodal tachycardia is a more frequent manifestation of digitalis intoxication than is paroxysmal atrial tachycardia with block.[2] This becomes more evident if the rate of a regularized nodal pacemaker in the presence of atrial fibrillation is considered to be tachycardia if over 70 per minute, as suggested by Dominguez.[7] Our incidence of n... cardia with block was 0.14 per ... tracings out of a total of 17,650

which is similar to 0.16 per cent of Dreifus and associates.[4]

One report has considered it to be three times more frequent than the atrial arrhythmia mentioned previously.[3] These same authors estimated that the incidence of that form of A-V tachycardia accompanied by conduction disturbances was in the range of atrial tachycardia with block.[3]

One source of error in the reported incidence of the arrhythmia under discussion lies in the fact that its different types of conduction disturbances have been classified under various headings. For instance, double nodal and ... onal nodal tachycardias have ... ncluded under this heading unt... [3] In addition an observer ca... verlook nodal tachycardia with ... occurs during atrial fibrillat... ware... f it. Evidently ... ed

simply as examples of auricular fibrillation.

The disturbance of rhythm was spontaneous in only one of our clinical patients who had a recent posterior wall myocardial infarction. In such cases it is not rare to find disturbances of A-V impulse formation and of impulse conduction.[7] Acute rheumatic fever is another cause of rapid nodal tachycardia, but is not present in this series since this disease is seen infrequently in our area.[11]

In spite of the fact that various clues and certain rhythms are very suggestive of digitalis intoxication, there are times when such a diagnosis is difficult to make. The acetyl strophanthidin tolerance test can be used in those instances. This test was performed in 4 different patients, and in all the deleterious effects were evident

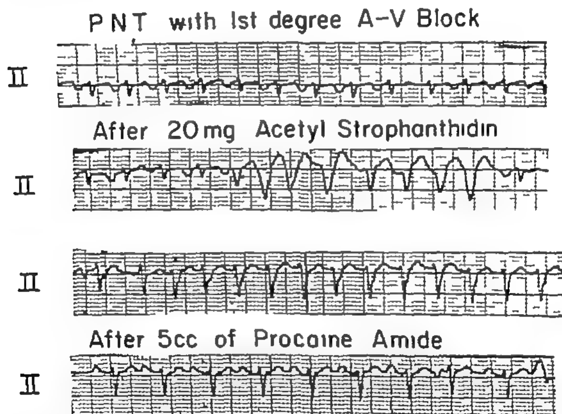


Fig. 4. Case 30: The effects of acetyl strophanthidin on nonparoxysmal nodal tachycardia with first-degree A-V block due to digitalis. The records were taken from a 72-year-old chronically digitalized patient with ASHD in whom the arrhythmia appeared during bronchopneumonia. Digoxin had been increased from 0.25 to 0.75 mg. daily. Inverted P waves can be observed in the upper strip. They are followed, after an interval of 0.15 sec., by a QRS complex of normal width. Therefore, the diagnosis of A-V nodal tachycardia with first-degree A-V block was made (rate 158 per min.). An acetyl strophanthidin test was carried out because some observers thought that the rhythm under discussion was a spontaneous coronary sinus tachycardia unrelated to digitalis. Five minutes after 0.20 mg. of acetyl strophanthidin, a short run of ventricular tachycardia appeared, interfering with the nodal arrhythmia. Although the third strip is not continuous with the previous one, it nevertheless shows the transition from the "upper" nodal tachycardia with A-V block to a faster middle nodal tachycardia. Simultaneous independent tachycardias, as well as an "upper" tachycardia of faster rate, can be excluded because no evidence of the large inverted P waves can be seen (there is no deformation of the T waves). However, inspection of the second QRS complex reveals that it is preceded by a small, nearly isoelectric, but definitely inverted P wave, which might indicate a different center of impulse formation. Finally, the lower strip shows conversion to sinus rhythm after 5 c.c. of procaine amide. The record as a whole emphasizes the transitions between the various types of digitalis-induced nodal tachycardia.

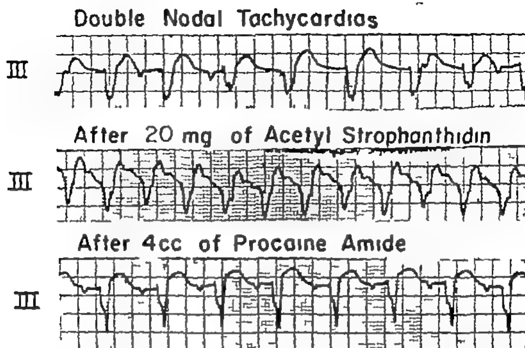


Fig. 5. Case 8. Effect of acetyl strophanthidin on double tachycardia produced by digitalis excess. The records were obtained from a 64-year-old patient with ASHD who had received a complete oral digitalization dose 24 hours before. Complete left bundle branch block had been present in the electrocardiograms for several years. The upper strip shows inverted P waves occurring at a rate of 80 per minute (nonparoxysmal nodal tachycardia). They are completely independent from the QRS complexes, and fall in different parts of the regular R-R cycles. In addition, regular bizarre QRS complexes which occur at a rate of 94 and measure 0.13 sec. can be seen. Note that both pacemakers are completely dissociated.[10] Were it not for the knowledge that the patient had pre-existing bundle branch block, the diagnosis of simultaneous A-V nodal tachycardias could not have been made; the first choice was independent A-V and ventricular tachycardias. An acetyl strophanthidin tolerance test was performed. After 0.20 mg. of acetyl strophanthidin, the P waves disappeared and the regular ventricular (nodal) pacemaker discharged at a rate of 160. No inference can be made as to what happened to the P waves, yet the increase in rate of digitalis-induced atrial or nodal rhythm after additional amounts of the same drug has been reported previously.[8] The lower strip was recorded after 4 c.c. of procaine amide had been administered. The drug was stopped because the patient showed slight hypotension. It can now be seen that the inverted P waves (rate 95) have reappeared (nodal tachycardia). They are followed after a P-R interval of 0.19 sec. (first-degree A-V block) by the same widened and bizarre QRS complexes which are characteristic of complete left bundle branch block. Whether the basic rhythm could have been re-established subsequently after larger amounts of Pronestyl is not definitely known. Nevertheless, sinus rhythm was recorded 24 hours later after no further therapy.

even with small doses. On the contrary, the effects of short-acting digitalis preparations in spontaneous ectopic supraventricular rhythms are most frequently characterized by the fact that large amounts can be administered without the appearance of premature ventricular contractions or tachycardia, the arrhythmia possibly reverting to a sinus mechanism.[1,19] However, the potential toxicity of digitalis should be kept in mind so that its use will not be considered routinely and only when the necessary precautions are taken.

Summary

The study of 36 cases of nodal tachycardia with block revealed that digitalis was the etiological factor in 29. Toxicity was estimated to be present in 27 of these 29 patients, but in 2 others it occurred as a transitional stage in the reversion of ectopic nodal tachycardias (without conduction disturbances). Nodal tachycardia was detected after initial digitalization in more than one half of the patients. When it appeared after operation, the arrhythmia was probably related to surgical trauma per se, since it was as frequent in digitalized

as in nondigitalized pre-surgical patients. Arteriosclerotic heart disease was the most frequent etiological cause in this group only one individual was not digitalized before the appearance of the arrhythmia.

The acetyl strophanthidin test was carefully performed in selected patients so as to determine whether the ectopic tachycardia was spontaneous or drug induced. Bizarre toxic rhythms were induced with small doses of this preparation thus permitting a differentiation from spontaneous tachycardias. The hazards of this drug should be kept in mind.

The infrequency with which rapid nodal rhythm with conduction disturbances has been described has been due in part to the fact that several of its forms have been classified under different headings, and in part, to the difficulty in making the correct diagnosis when varying exit blocks coexisted with atrial fibrillations. In such cases the tracings might be considered simply as instances of fibrillation with irregular response.

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Complex cardiovascular malformations associated with the corrected type of transposition of the great vessels

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Corrected transposition of the great vessels (CTGV) is usually associated with other cardiovascular defects such as interventricular septal defects or interauricular septal defects,[1,2] or both combined. Pulmonary stenosis,[3] patent ductus arteriosus, or Ebstein's malformation of the left atrioventricular valve[4] have also been reported in association with CTGV. More complex associated malformations render the CTGV very difficult to recognize in vivo. Whatever the associated malformation, regardless of whether the transposition is truly corrected from the functional standpoint, the anatomic diagnosis is possible if one bears in mind the embryologic basis of CTGV.

Some types of tricuspid atresia and single ventricle which simultaneously exhibit transposition of the great vessels, and some cases of persistent truncus arteriosus have certain angiocardiographic and sometimes electrocardiographic features which permit the recognition of the corrected type of transposition. Obviously, in a persistent truncus arteriosus there is no true transposition of the great vessels (TGV), but the features which pertain to the corrected position of the ventricles apply to this entity. It seems worth while to report 5 such instances and to emphasize the possibility of recognizing this peculiar combination of malformations.

Case reports

Case 1. Z.R.P. (H 51501), a 17-year-old girl, was born of a full-term pregnancy and normal delivery. She had been cyanotic from birth. Dyspnea on effort and squatting were present at an early age. Physical examination revealed a Grade 3+ cyanosis with marked clubbing of the fingers and toes. The apex impulse was felt in the fifth left intercostal space 1 cm. to the left of the mid-clavicular line. The aortic impulse was clearly felt at the suprasternal notch. On auscultation there was a soft continuous murmur in the second right intercostal space and the infraclavicular area. The second pulmonic sound was pure and of normal intensity.

X-RAY EXAMINATION. The frontal view disclosed Grade 1+ cardiomegaly; the middle left segment was concave, and the apex was turned upward. In the right anterior oblique view a Grade 1+ enlargement of the right ventricle was recognized. In the

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left anterior oblique view the left ventricle was thought to be enlarged. Hilar vascularity was increased.

ELECTROCARDIOGRAPHY. The electrocardiogram showed +150-degree axis deviation and was suggestive of right auricular enlargement. A thoracic circle showed ventricular morphologies suggestive of biventricular enlargement, and it was compatible with transposition of the ventricles, i.e., qR type of complexes were recorded over the right hemithorax, whereas widely diphasic RS complexes were recorded from the left hemithorax.

Cardiac catheterization disclosed a high right ventricular pressure 99 mm. Hg systolic and peripheral arterial unsaturation.

ANGIOCARDIOGRAPHY. Opaque substance was injected into the right atrium, from which it entered a right-sided ventricle which showed a smooth inner surface unlike a true right ventricle. Thereafter a single vessel was filled whose left border was coincident with the left border of the cardiac outline. This vessel was directed to the right and descended on the right side of the trachea. The opaque substance also entered the left-sided ventricle through a ventricular septal defect; this ventricle exhibited a trabeculated inner contour such as is commonly seen in anatomically right ventricles (Fig. 1,B). From the posterior aspect of the single vessel two smaller vessels emerged, both of which entered the right lung.

These studies seem to substantiate the diagnosis of *persistent truncus arteriosus with probable transposition of the ventricles.*

Case 2. P. H. R. (INC-63442), a 3-month-old adopted baby girl, was born of a normal full-term pregnancy. The child's mother was known to have purposely attempted abortion. The patient weighed 2,800 grams at birth and was not cyanotic. When she was 4 days old, she became cyanotic and dyspneic. At the age of 20 days she suffered an infection of the lower respiratory tract and was referred to the Instituto Nacional de Cardiología in Mexico City. Physical examination disclosed a dyspneic, chronically ill female infant with Grade 3+ cyanosis. Extreme dyspnea interfered with adequate examination, but tachycardia and gallop rhythm were present. The pulmonic second sound was markedly accentuated. No murmurs were discernible. The blood pressure was not taken.

X-RAY EXAMINATION. The x-ray films disclosed a small heart with a wide pedicle. On barium swallow the opaque substance followed a normal course to the level of the heart, but occupied a right-sided position in the stomach. The left middle segment (pulmonary segment) appeared to be concave, and the vascularity of the lungs was thought to be normal or even increased.

The electrocardiogram showed extreme right axis deviation (−120 degrees) and negative P waves in Lead I. The rS type of ventricular complexes in all the precordial leads suggested the pattern seen in cases of *single ventricle.*

The complete blood count revealed 7,300,000 red blood cells and a hemoglobin of 18 Gm.

The patient died after several episodes of hypoxia which followed a gastrointestinal infection and dehydration.

The findings mentioned suggested the diagnosis of levocardia with probable transposition of the great vessels. In other words, the abdominal viscera and the auricles were transposed.

Autopsy in this case (No. 2165) disclosed the following features. The liver was placed on the left and the stomach on the right side, i.e., there was

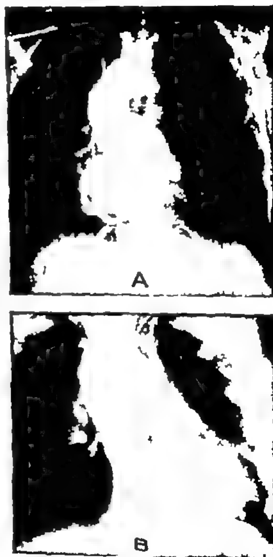


Fig. 1. Comparative angiocardiographic study depicting a classic example of a persistent truncus with the ventricles placed normally to the left (*A*), and a case of persistent truncus with transposition of the ventricles to the right (*B*). Notice that in the first case the single vessel occupies the middle portion of the cardiac shadow, whereas in the second case the vessel ascends along the left cardiac contour; the aortic arch and the descending portion of the vessel are placed to the right. In this case the radio-opaque substance entered the left-sided ventricle through a ventricular septal defect. Notice the trabeculated aspect of this chamber.

t spos tis of the bdominal sceera. The heart w normally placed i t pex was directed t the left nd t was loc ted i the left hemithor x. There was single essel arising from the right border of the heart which described conve arc t the right Both pulmonary rteries rose directly from the single essel The t ium plac d on the right recen ed the four pulmonary eins, and the tri m placed on the left recei ed the two enae ca ae (Fig 2). I ternall the trium placed on the right showed the features f th anatomically left trium i e it was smooth, it did not ha e a crista terminalis,



Fig 2 Case 2 A The anatomicall left trium receiving the pulmonary eins (*see rrow*) is placed t the right. Notice the muscular band, the only remna t of the trial septum. *B* The natomically right entricle, placed t *the right, from hich arises the single essel in front of the crist. supra entricularis The entricular* wall is thick. *C*, The natomically right auricle recei ing both enae superior ena cava is pointed out by the indicator) is placed t the left in relation ith the nator icle. Notice the smooth ppearance of the left septal surface the fine trabecu of li pical tricular septal defect nd the common trioventricular val

and, again, it received the four pulmonary veins. The interatrial septum was almost completely absent it was represented by a thin muscular band which was oriented sagittally in the midline about 2 mm. above the annulus of the trioventricular valves. There was a common trioventricular orifice formed by three valves one was anterior and two were posterior and smaller one to the right and one to the left. The ventricle on the right side was trabeculated, it exhibited the crista supraventricularis and it was hypertrophic. In front of the crista supraventricularis, a single vessel emerged, which showed four semilunar sigmoid valves cusps of normal appearance. There was a large ventricular septal defect, the upper limit of which was semilunar and it was constituted by the upper border of the interventricular septum. This defect was continuous with the suprajacent atrial septal defect (trioventricularis communis).

The atrium placed to the left showed the features which pertain to the anatomically right atrium, i.e., there was crista terminalis the venae cavae entered into it. The ventricle placed on the left showed fine trabeculae, smooth septal surface and normal thickness of its wall. All of these features are those normally present in the anatomically left ventricle.

In summary, the anatomic diagnosis was (1) Levocardia with situs inversus viscerum. The cardiac apex was directed to the left, and the heart occupied the left hemithorax. The atria were transposed. (2) Transposition of the ventricles with respect to the position of the atria, the anatomically right ventricle was placed to the right (normally for this type of levocardia it should be placed to the left), and the anatomically left ventricle was placed on the left (it should be placed on the right side for this type of levocardia). (3) Persistent truncus arteriosus. (4) Common trioventricular canal of the complete variety.

Case 3. M. B. (H 100032), a 17-year-old girl, was born of a normal full-term pregnancy and normal delivery. She was asymptomatic until the age of 7 years, at which time dyspnea and short, stabbing precordial pains appeared. A congenital heart condition was diagnosed at that time. Simultaneously, cyanosis appeared. When examined, she complained of minimal dyspnea and frequent rapid palpitations of short duration. She led a normal life.

On physical examination the patient appeared to be in general good health, without dyspnea, but with Grade 2+ cyanosis of the fingers, toes, and lips. The blood pressure was 110/70 mm. Hg. The apex beat was felt in the fifth left intercostal space. There was palpable closure of the pulmonary valve and a soft, protosystolic Grade 2 murmur which was preceded by a protosystolic snap over the pulmonic area. The pulmonic second sound was "pure" and accentuated. The rest of the examination was not contributory.

ELECTROCARDIOGRAPHY. The electrocardiogram was suggestive of left atrial and ventricular enlargement.

X-RAY EXAMINATION. The frontal view disclosed moderate cardiomegaly. The middle segment was straight and the hilar vascular markings were increased. In the left anterior oblique view the ventricles contracted synchronously. The left ventricular border was somewhat displaced upwardly and the vascular pedicle appeared to be wider than normal.

ANGIOCARDIOGRAPHY. Opaque substance was injected into the left atrium which was entered through an atrial septal defect. From this chamber a single ventricle was filled, which showed thick walls



Fig. 5. Angiocardiogram in Case 3. The frontal view (A) depicts a single ventricular chamber from which the aorta, placed to the left, and the pulmonary artery, placed to the right, are filled. The aorta forms the left border of the cardiac contour. The aortic arch is placed on the right. In the left lateral view (B) the aorta is seen in front of and parallel to the pulmonary artery.

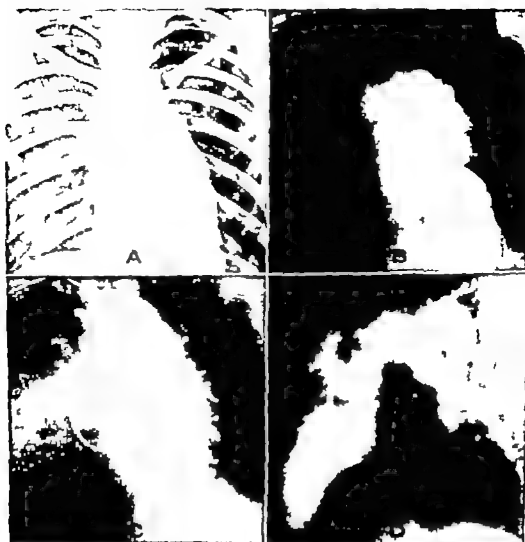


Fig. 4, *A-D*. X-ray film and angiocardiograms in Case 4. *A*, Notice the normal size of the heart in the frontal view and the prominence of the middle segment which continues the left inferior cardiac contour. *B* and *C*, Angiocardiograms in frontal view show the filling of the single ventricular chamber from which both vessels arise in a parallel fashion, the aorta to the left and the pulmonary artery to the right. *D*, The left lateral view depicts an anterior aorta and a very much dilated and posterior pulmonary artery. (For Fig. 4,*E* and *F* see opposite page.)

A ventricular septum was not visualized. Thereafter the two great vessels filled simultaneously; the aorta, placed to the left, formed the left contour of the cardiac shadow and arched to the right (Fig. 3,*A*); the pulmonary artery was very much dilated and was placed to the right and behind the aorta. Its valves appeared at a lower level than the aortic valves. In the left lateral view both great vessels ran parallel; the aorta was the anterior vessel (Fig. 3,*B*).

The final diagnosis was: (1) single ventricle, (2) transposition of the great vessels with the arrangement which pertains to the "corrected" variety, and (3) atrial septal defect.

Case 4. P.A.M. (11-090792), an 18-year-old boy came for consultation because he had suffered from dyspnea on effort and palpitation in the last few years. Physical examination disclosed a slightly cyanotic patient with minimal clubbing of the fingers and toes. The apex beat was felt in the fifth left intercostal space at the level of the mid-clavicular line. A harsh systolic thrill which was felt in the second left intercostal space extended to the midprecordial and left infraclavicular areas. A harsh Grade 4 systolic murmur was heard over the pulmonary area and was transmitted to the vessels of the neck. The second pulmonic sound was accentuated.

X-RAY EXAMINATION. The heart was of normal size in the frontal view. The middle segment was prominent, and was continuous with the remainder of the left lower border of the cardiac contour. The hilar

essels and the pulmonary transparency were normal (Fig. 4,*A*). In the right anterior oblique view the right entricle appeared to be slightly enlarged, and the cardiac pedicle to be widened. In the left anterior oblique iew the right atrium was slightly enlarged.

ELECTROCARDIOGRAPHY. The electrocardiogram showed right axis deviation (+135 degrees). The P waves were peaked and tall in Leads II and aV. A thoracic circle showed left ventricular morphologies with hypertrophy over the right hemithorax, and right entricular morphologies over the left hemithorax, also with hypertrophy and systolic overloading (Fig. 4). This was suggestive of transposition of the ventricles and biventricular hypertrophy.

CARDIAC CATHETERIZATION. Gas analysis showed step-up at the level of the right-sided entricle, and peripheral arterial unsaturation. The pressure in this entricular chamber and that in the aorta were identical. The aorta was entered from the right-sided entricle the catheter ascended in close proximity to the left border of the cardiac contour which suggested that the aorta arose in an abnormal position.

ANGIOCARDIOGRAPHY. This study depicted the filling of what appeared to be single entricle, from which both great vessels emerged, the aorta anterior and to the left and the pulmonary artery posterior and to the right. The vessels appeared to be parallel and did not cross each other (Fig. 4, *B*,*C*,*D*).

The following conclusions were reached (1) single entricle, and (2) transposition of the great essels arranged in the manner observed in the "corrected" type of transposition.

Case 5. C.A.I. (H-086140), 25-year-old man, had past history which was noncontributory except for the fact that cyanosis and clubbing appeared t ery early age. He claimed not to have dyspnea. On physical examination the apex beat was felt in the sixth left intercostal space, 2 cm. outside of the mid-clavicular line. The precordial area was bulging; he had pigeon-breast thorax. There was soft systolic thrill within the pex. On auscultation there was Grade 2 systolic murmur t the midprecordial and endoapical areas. It as not transmitted. The second pulmonic sound was loud and pure.

X-RA EXAMINATION. The frontal view disclosed Grade 2+ to 3+ cardiomegaly. The middle segment was conca the vascularity of the lungs was greatly increased the hilar essels showed vigorous pulsations. The aortic arch descended on the right (Fig. 5,*A*). I the right terior oblique view the left trium was slightly enlarged. I the left anterior oblique view the left ventricle was enlarged to Grade 3+ and the right trium to Grade 2+. In this position the cradiac pedicle was idar. The contour of essel was noticed which seemed to prolong pward the nteroinferior border of the cardiac contour (Fig. 5,*B*).

ELECTROCARDIOGRAPHY. The electrocardiogram showed left axis deviation (−45 degrees) and peaked P waves in Leads I and II. It was suggestive of right and left trial enlargement and left entricular hypertrophy.

CARDIAC CATHETERIZATION. The right ventricular chamber was not entered. The catheter entered the left trium with great ease, from whence it was advanced into the left ventricle. The great vessels were not catheterized. There was arterial unsaturation.

ANGIOCARDIOGRAPHY. The opaque substance was seen to pass from the right to the left atrium through large septal defect. The left entricular chamber filled immediately afterward. It appeared to be hypertrophic. From this chamber both great essels filled, the aorta placed anteriorly and to the left, constituting the left border of the cardiac contour and then crossing over to the right side. The pulmonary artery was placed posteriorly and to the right. The right-sided ventricular chamber never filled. Instead

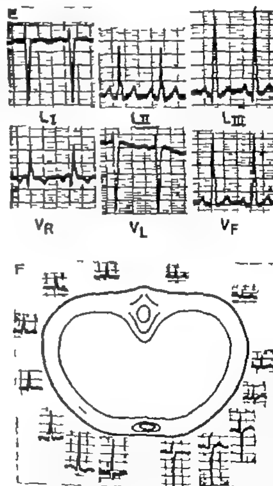


Fig. 4. *E* and *F*, *E*, Electrocardiogram in Case 4. The study of the P wa indicates that the tria are normally placed. There is evidence of right trial enlargement. The morphology of the entricular complex is of the qRs type with plus-minus T was which corresponds t variations in potential of hypertrophic left entricle placed on the right. Rs complexes with positive T es registered in Leads V and V correspond t variations in potential of hypertrophic anatomic right entricle (systolic overloading).

mpty triangular re visible which w limited on the right side b the right trium on the left by the left-sided entricle nd below by the diaphragm (Fig 5 C D)

The final diagnosis wa (1) treslu of the right sided trioventric la al e (t icuspid?) trial sept l defect hypertrophy of the left-sided entricle (2) t nsp sition of the great essels, both essel rising from th hypertrophic entricula hamber f the f shion observed in the orrected" type and (3) probable t sposition of the entricles.

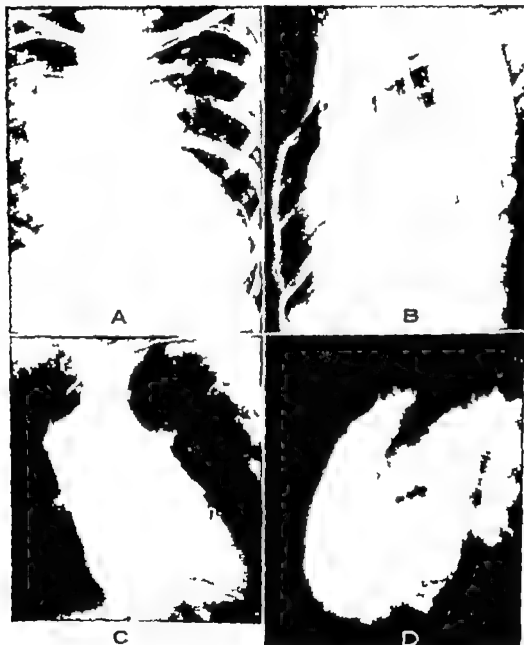


Fig. 5 X-ray films nd angiocardiogram in Case 5 A N tic the cardiomeg ly the incr sd left inferior cardiac border the prominent aortic knob t the right nd increased hila nd scular markings. *B* Left terior oblique iew showing the enlargement of the left ventricle nd the right tricle the wide cardiac pedicle nd the prolong tion of the nteroinferior ardiac border upward by the contou of a essel. *C*, Angiocardiogram in the frontal iew show ing the filling of both tria and the hypertrophic left-sided entricle from which both essels rise in par llel fa hion, the aorta t the left nd the pulmonary artery t the right *D* The later l iew depict the anterior aorta nd posterior pulmonary artery this latter vessel i very much dilat d.

Case 4 E.C.B (# 82774). 13-year-old boy who was known to have been cyanotic since birth was seen at the Instituto Nacional de Cardiología in Mexico City. Although he had poor tolerance to exercise, he was never critically ill. His body build was reminiscent of that described in Marfan syndrome.

PHYSICAL EXAMINATION. He appeared to be markedly cyanotic and had marked clubbing of the fingers and toes. A Grade 2 systolic murmur was heard over the left sternal border and the second sound over the pulmonary area was accentuated.

X-RAY EXAMINATION. The heart was slightly increased in size; there was a right-sided aortic arch; the left middle segment was straight. No chamber appeared to be enlarged. The pulmonary fields appeared to be overtransparent (Fig. 7).

ELECTROCARDIOGRAM. There was left axis deviation and right bundle branch block; the tracing was suggestive of left ventricular hypertrophy (Fig. 7).

With these findings the possibility of corrected transposition of the great vessels was considered. Angiocardiography and catheterization were recommended.

The angiocardiogram was not conclusive. However, during the test it was seen that the catheter oscillated amply within the ventricular chamber (selective angiocardiography) and the possibility of a single ventricle was raised.

Catheterization findings were as follows: (1) the right ventricular pressure was 90/10 mm. Hg; the infundibular right ventricular pressure was 47/11 mm. Hg; the pressure in the pulmonary trunk was 14 mm. Hg (mean). A pulmonary vein was entered through an atrial septal defect; the aorta was entered via the right ventricle and the pressure therein was 84/51 mm. Hg.

This information was found to be compatible with the diagnosis of an overriding aorta and pulmonary stenosis, that is, with the general picture of a tetralogy of Fallot. Again, the diagnosis of transposition of the great vessels was entertained since it was not in disagreement with the above-mentioned findings. An atrial septal defect was obvious, and a single ventricle was again mentioned as a good possibility.

The patient was operated upon for improvement of pulmonary circulation and possibly for total correction of malformations.

When the heart was exposed it was seen that the great vessels were transposed and that the aorta was at least four times the size of the posteriorly placed pulmonary artery. Through a ventriculotomy the following findings were made: (1) single atrium; (2) single atrioventricular valve (? was A-V communis); (3) large ventricular septal defect; (4) markedly trabeculated "left" ventricle from which both the aorta and the pulmonary artery arose.

Correction of any of these defects was thought to carry excessive risk, and the operation ended as an exploratory procedure. The patient recovered and had an uneventful postoperative course.

The final diagnosis was corrected transposition of the great vessels, common trilocular heart, and pulmonary stenosis.

Discussion

The anatomic basis of CTGV for a normally placed heart is as follows: the atria are normally placed, that is, the anatomically right atrium is on the right side and the anatomically left atrium is on the left side. The right atrium receives the venae cavae and the coronary sinus; the left atrium receives the four pulmonary veins. The ventricles are transposed, that is, the right-sided ventricle is the anatomic left ventricle, and the left-sided ventricle is anatomically the right one. Finally, the great vessels are transposed, i.e., the aorta is anterior and arises from the left-sided ventricle in front of the crista supraventricularis, and the pulmonary artery is posterior and placed to the right of the aorta, emerging from the right-sided ventricle parallel to the aorta.

The embryologic basis of this malformation is the abnormal torsion of the bulboventricular loop, inversely to that which takes place in a normal heart (Fig. 6)—hence the left-sided convexity of the loop. The anatomic result is the inversion of the ventricles, since the bulbus cordis will remain on the left side and will give rise to the anatomically right ventricle. Likewise, the primitive ventricle which gives rise to the anatomically left ventricle will now be placed on the right side. The anatomically right ventricle will remain the anterior of the two ventricles, whereas the anatomically left ventricle will continue to be, as in the normal heart, the posterior ventricle. Therefore, the truncus-conus which will give rise to the aorta and the pulmonary artery will be placed on the left, and it will be continuous with the bulbus cordis in a reverse position. This abnormal position of the truncus is that which in earlier stages of embryonic development is normal prior to its leftward displacement to the midline due to the normal disappearance of the conoventricular ridge.

TGV is due to the straight development of the truncoconal ridges, the result of which is that the fourth aortic arch will be continuous with the anterior ventricle (the anatomically right ventricle placed to the left). Another consequence of this abnormal development of the truncoconal ridges is that the sixth aortic arch, which

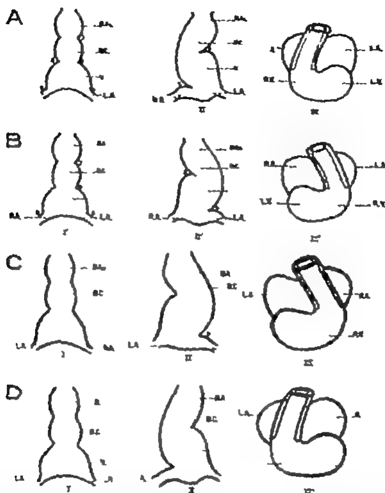


Fig. 6. Diagram of the torsion of the primitive cardiac tube. *A.* Normal torsion of the cardiac tube with its convexity directed to the right and its concavity directed to the left. *I.* At *1* and *2* the right and left interbulbar grooves are seen; *3* and *4* are the bulboventricular grooves; *5* and *6* correspond to the atrioventricular grooves. All of these limit the different portions of the primitive tube: bulbus aorticus (*B.Ao.*), bulbus cordis (*B.C.*), ventricle (*V.*), and primitive atria (*R.A.* and *L.A.*). *II.* The torsion of the cardiac tube is initiated because of the enlargement of grooves *4* and *5*. *III.* The torsion has been completed and the atria occupy their definitive position. The truncus continues the bulbus cordis on the right side of the heart. It was not divided normally because of the absence of the truncoconal ridges. The anatomic result is a persistent truncus in a heart with normally placed chambers. *B.* This diagram depicts the abnormal torsion of the bulboventricular loop with left-sided convexity and right-sided concavity due to an increase in grooves *3* and *6*. The truncus continues the bulbus cordis which is placed to the left (*III*); the truncus is not divided because of failure of development of the truncoconal ridges. The anatomic result [illegible] common trunk with inverse position of the ventricular chambers. *C.* This diagram depicts the normal torsion of the bulboventricular loop in a heart with mirror-image dextrocardia and some type of levocardia (that with atrial inversion). *I.* The primitive left atrium is placed to the right, and the primitive right atrium to the left. *II.* The normal torsion in this case is due to enlargement of grooves *3* and *6*. *III.* The torsion has been completed and the atria and ventricles occupy their definitive position. The truncus continues the bulbus cordis on the left side. It is not divided, for which reason the anatomic result is a common trunk in a heart with mirror-image dextrocardia or some type of levocardia. *D.* The abnormal torsion of the bulboventricular loop in a heart with mirror-image dextrocardia or some type of levocardia. The convexity is right-sided because of an increase in grooves *4* and *6* (*II*). In *III* the torsion has been completed; the truncus continues the bulbus cordis which is placed to the right. The truncus contus is not divided. The anatomic result is a common trunk with inverse position of the ventricular chambers in a heart with mirror-image dextrocardia or some type of levocardia. (Modified from Davis,[10] Kramer,[12] and de la Cruz.[19])

is a posterior vessel, will be continuous below with the anatomically left (or posterior) ventricle. Thus, the aorta will arise from the anatomically right ventricle placed on the left side and the pulmonary artery will arise from the anatomically left ventricle placed to the right the aorta is anterior and the pulmonary artery is posterior but, unlike the usual complete transposition of the great vessels, the aorta will be placed on the left and the pulmonary artery on the right Now then if the aorta is placed on the left, we may correctly assume that the ventricle from which it emerges, placed also on the left side, is the anatomically right ventricle If so the transposition is of the "corrected type Such anatomic features have been present in reported cases with autopsy confirmation.[18]

If the embryologic mechanism for transposition is present while the primitive truncus-conus never becomes divided the result is a transposition of the ventricles with a persistent truncus (Fig 7,B)

Normally the truncus-conus undergoes a left lateral displacement and eventually occupies a medial position where the truncoconal septum and the interventricular septum coincide and fuse The opposite will take place if the bulboventricular loop curves to the left, in which case the truncus-conus will advance from a left lateral position to a medial position. For this reason in transposition of the ventricles, the undivided truncus-conus occupies either a left position or a medial position but not a right-sided position as in the ordinary type of persistent truncus arteriosus communis (see Fig 1,A)

In our Case 2 the autopsy showed levocardia, and the atria were transposed (in a position pertaining to dextrocardia) in other words, the anatomically right atrium was placed to the left and in relationship with an anatomically left ventricle, whereas the anatomically left atrium was placed to the right and was related to an anatomically right ventricle. According to de la Cruz and associates,[8] in such a type of levocardia there is an abnormal torsion of the bulboventricular loop in a sense opposite to that normally seen for the atria in this type of levocardia this gives rise to the inversion of the ventricles. Furthermore, in our case there was no partition of the truncus-conus for which reason the result was a persistent truncus arteriosus communis which arose from the anatomically right ventricle in front of the crista supraventricularis, following the right border of the heart. This type of truncus is commonly seen in levocardia with transposition of the atria or in mirror image dextrocardia with inversion of the ventricles due to abnormal torsion of the bulboventricular loop (Fig 6,D)

Case 1 corresponds to a case of persistent truncus in a normally placed heart. It is also seen in cases of dextrorotation with normally placed atria complicated by abnormal torsion of the bulboventricular loop. The latter complication gives rise to inversion of the ventricles such as that seen in TCGV save for the fact that there is only one vessel and not two

The same reasoning could be applied in cases of single ventricle i.e. in a heart in which the bulboventricular loop has bent normally the interventricular septum may be lacking with a resulting single ventricle. Likewise the interventricular septum may be absent in a heart in which the bulboventricular loop was abnormally bent to the left. The disposition of the great vessels, i.e anterior and left-sided aorta with posterior and right-sided pulmonary artery will give the clue to the abnormal torsion which the bulboventricular loop underwent, and which resulted as it were in a transposition of the "ventricles. This is quite different from the cases of single ventricle with TGV in which the bulboventricular loop was normally bent Here the aorta is anterior but simultaneously it is on the right side and the pulmonary artery is posterior but on the left side.[19]

Both the usual type and the corrected" type of transposition of the great vessels associated with single ventricle have been reported, proved either at autopsy or angiocardiographically[18] with or without pulmonary stenosis. Edwards[17] has described this latter type (CTGV) associated with single ventricle and normal pulmonary artery

The electrocardiographic behavior of single ventricle is quite interesting[18] If TGV is present, qRs morphologies of the



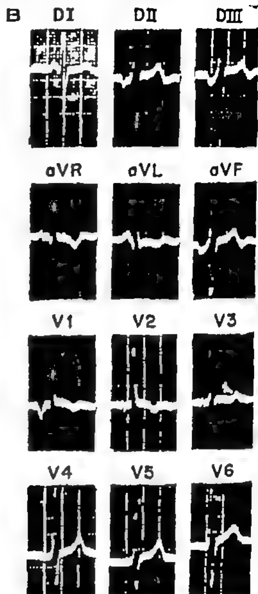


Fig. 7. Case ... A, ... the left border of the heart. Its upper segment is formed by the aorta ... the right ... pulmonary ... B. The electrocardiogram shows right ventricular hypertrophy.

...ventricular complexes are seen in the right precordial leads (V... and V...). RS complexes in Lead V... and V..., and ... complexes in Le... V... and V.... This may be interpreted as ... of transposition of the morphologies of the ventricles and it is a frequent finding in the "corrected" type of transposition, which is to be accounted for by the inversion of the ventricles. Our fourth case is an example of a single ventricle which shows this type of electrocardiographic behavior. However, ventricular activation in cases of single ventricle is not clearly understood in view of the absence of an interventricular septum. The ventricular complexes in these cases could be accounted for by the transposition of the morphologies of each ventricle if these cavities are actually transposed, although there is no ventricular septum.

In tricuspid atresia with TGV and normal pulmonary artery, the aorta is anterior and on the right side. It arises from

the hypoplastic right ventricle whereas the pulmonary artery is posterior on the left side and arises from the left ventricle. In our case with atresia of the right atrioventricular valve atrial septal defect, and hypertrophy of the left-sided ventricle TGV was clearly discernible However the aorta was anterior but on the left side emerging from the left-sided ventricle and the dilated pulmonary artery was posterior and on the right side, emerging from the same ventricle Since the aorta is anterior in this case the ventricle from which it emerges is also anterior This automatically leads to the diagnosis of anatomically right ventricle as can only be the case in instances of corrected transposition of the great vessels.

A similar case with pulmonary stenosis reported by Kjellberg and associates showed tricuspid atresia and CTGV with an anterior and left-sided aorta arising from the hypertrophic ventricle placed on the left.

Summary

Abnormal torsion of the bulboventricular loop such as is seen in corrected transposition of the great vessels (CTGV) *may* be present in a number of complex malformations including single ventricle and persistent truncus arteriosus. Our 6 cases illustrate this point.

The diagnosis may be reached by means of angiocardiography which will show the peculiar disposition of the great vessels, i.e. the aorta anterior and on the left side, and the pulmonary artery posterior and on the right side. On occasion angiocardiography will permit the recognition of transposition of the ventricles because of the peculiar inner contour of each chamber In other instances, the electrocardiogram will permit recognition of the inversion of the ventricular chambers through the study of the unipolar ventricular morphologies.

The associated malformations may be recognized simultaneously by the very same methods and the clinical and hemodynamic behavior of each case.

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Experimental and laboratory reports

Cardiac effects of synthetic oxytocin (Syntocinon)

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In 1952 Morris, Thornton and Harris[1] reported that obstetrical patients treated with oxytocin failed to demonstrate any electrocardiographic abnormalities during cyclopropane anesthesia. On the basis of this observation, the potential antiarrhythmic activity of oxytocin has been investigated in a variety of experimental situations in which cardiac arrhythmias are produced. For example (a) Feldman and Forgaard[2] reported that oxytocin could prevent or reduce the duration of ventricular arrhythmias in cyclopropanized dogs challenged with epinephrine (b) Panisset and Beaulnes[3] were able to terminate arrhythmias induced by chloroform epinephrine in dogs, and atrial and ventricular fibrillation produced in the isolated rabbit heart by electrical stimulation (c) Melville and Varma[4] found that oxytocin could prevent electrocardiographic changes due to myocardial hypoxia and could terminate ventricular fibrillation produced by injection of picrotoxin into the lateral ventricle. However these workers were not able to prevent ventricular fibrillation produced by toxic doses of ouabain. On the other hand Bircher Kanai and Wang[5] were able to convert cardiac arrhythmias due to deslanoside as well as those due to pentylenetetrazol and picrotoxin. The basic mechanism responsible for the antiarrhythmic activity of oxytocin is not known. However it has been suggested that this hormonal agent possesses a quinidine-like action. In order to test this hypothesis, a series of experiments was instituted in which the effect of oxytocin on the basic electrophysiologic properties of cardiac muscle was studied. These data then were compared with previous results obtained with quinidine. In view of the results obtained in these initial studies, the potential efficacy of oxytocin as an antiarrhythmic agent in hypothermia was investigated. The results of these investigations form the basis for this communication.

Methods

Isolated atria Adult cats were anesthetized with pentobarbital sodium (30 mg./Kg intraperitoneally) the thorax was opened and the entire heart was removed and placed in a beaker of Krebs-Henseleit solution Both atria were dissected away from the heart attached to a muscle holder and immersed in a chamber which contained Krebs-Henseleit solution aerated with 95 per cent oxygen and 5 per cent carbon dioxide and maintained at a temperature of 37°C The experimental design was similar to that described previously.[6] Electrograms and myograms were obtained simultaneously on a Tektronic Twin Beam oscilloscope and photographic records were obtained periodically

Rate and amplitude of contraction were

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Address Astra Pharmaceutical Products, Inc., Neponset St., Worcester 6, Mass.

Table I. Effect of various concentrations of oxytocin on the rate and contractility of isolated rabbit atria

Oxytocin concentration (mU./ml.)	Rate (beats/min.)		Amplitude of contraction (mm.)	
	Pre	Post	Pre	Post
0	153 ± 9 5	153 ± 9 5	19 6 ± 0 09	19 6 ± 0 09
15	143 ± 5 9	145 ± 5 9	12 6 ± 0 07	13 0 ± 0 1
30	139 ± 13 7	156 ± 10 8	13 7 ± 0 09	14 3 ± 0 12
60	149 ± 6 7	145 ± 4 7	12 3 ± 0 09	13 0 ± 0 15
90	165 ± 5 8	137 ± 3 5	16 6 ± 0 06	16 5 ± 0 09

*Significant at the [illegible] level (Student [illegible] test).
Each figure represents the mean ± standard error of three experiments before (Pre) and after (Post) 30 minutes of exposure to oxytocin.

measured at 30-minute intervals for a period of 2 hours in three control untreated atria and in groups of three atria which were exposed to oxytocin (Syntocinon) in concentrations of 15, 30, 60, and 90 milliunits per milliliter.

Papillary muscle. Papillary muscles were removed from the right ventricle of cats anesthetized with pentobarbital sodium (30 mg. kg. intraperitoneally), attached to a muscle holder, and immersed in a chamber which contained Krebs-Henseleit solution aerated with 95 per cent oxygen and 5 per cent carbon dioxide and maintained at a temperature of 37°C. A description of the muscle holder and the method for recording electrical and mechanical events has been presented previously. Measurements of diastolic threshold, amplitude of contraction, refractory period, and conduction velocity were made at 30-minute intervals in five control muscles and in groups of five muscles exposed to 5, 10, 15, and 30 milliunits per milliliter of oxytocin. Fresh papillary muscles were used for each concentration of drug. Thus, no possibility of a cumulative effect of the drug existed.

Intact dog. Adult mongrel dogs were anesthetized with pentobarbital sodium (30 mg./kg., intravenously). Hypothermia was induced in all dogs by immersion in an iced water bath of 2 to 5°C. Electrocardiograms (Standard Limb Lead II) and arterial blood pressure were recorded prior to and periodically during hypothermia and were monitored continuously on an oscilloscope. Rectal temperature was measured continuously with a thermistor, and heart temperature was determined at the conclusion of the experiment by a mercury thermometer placed in the left ventricle. All animals were ventilated artificially when rectal temperatures reached 30°C. The experiment was concluded when either ventricular fibrillation occurred or no electrocardiographic activity was seen for a period of 10 consecutive minutes (asystole). The incidence of ventricular fibrillation in control untreated dogs and that in oxytocin-treated animals were compared on a statistical basis.

Results

Isolated atria. The atrial rate and amplitude of contraction remained remarkably stable during the 2 hour experimental period in the control untreated atria (Table I). Moreover, no significant change in these two variables was observed in the groups of atria exposed to 15, 30, or 60 milliunits per milliliter of oxytocin. At a concentration of 90 milliunits per milliliter of oxytocin, a significant fall in atrial rate did occur. After 2 hours of exposure to this concentration of oxytocin, the mean rate was 137 ± 3 5 beats per minute, as compared to the control rate of 165 ± 5 8 beats per minute (p = <0 01). The amplitude of contraction, however, was unaffected by this concentration of oxytocin (Table I). No change in height, duration, or contour of the surface action potential was noted in either the control or oxytocin-treated atria. Thus, the fall in atrial rate after exposure to 90 milliunits per milliliter

of oxytocin was the only change noted in any of the atrial preparations which were studied.

Papillary muscle The effect of oxytocin on isolated ventricular muscle was then investigated using the cat papillary muscle driven at a constant rate of 30 beats per minute. The results are summarized in Table II All of the papillary muscles, untreated as well as treated preparations showed a slight rise in diastolic threshold during the 2 hour experimental period However the increase in threshold was not significant at the 0 05 level in any of the groups. Thus, oxytocin per se produced no change in ventricular threshold With respect to the amplitude of contraction no significant alternation occurred in the control muscles or in those exposed to 5 and 10 milliunits per milliliter of oxytocin However at concentrations of 15 and 30 milliunits per milliliter a 30 per cent increase in the amplitude of contraction did occur which was significant at the 0 01 level (Table II)

The comparative effects of oxytocin on conduction velocity and absolute refractory period were of particular interest Conduction velocity was not changed significantly by any concentration of oxytocin However the absolute refractory period did exhibit definite alterations. In the control muscles and those exposed to 5 milliunits per milliliter of oxytocin no change in the absolute refractory period was observed At a concentration of 10 milliunits per milliliter of oxytocin the absolute refractory period showed a slight but significant increase of approximately 6 per cent. At concentrations of 15 and 30 milliunits per milliliter the absolute refractory period was increased by approximately 28 per cent (p = <0 01) Thus, although no change in conduction velocity was produced by oxytocin this hormonal agent did cause a significant prolongation of the refractory period

Intact dog Ten of the 12 control dogs (83 per cent) which were rendered hypothermic developed ventricular fibrillation at a mean rectal temperature of 19 2 ± 5 8°C This frequency of ventricular fibrillation in control untreated hypothermic dogs agrees favorably with previous results in hypothermic dogs In the initial series of treated dogs, oxytocin was administered intravenously in a dose of 2 I U per kilogram at 30-minute intervals. The injections were started when the rectal temperature had fallen to 30°C and were continued until either ventricular fibrillation or asystole occurred Three of 7 dogs (43 per cent) treated in this fashion developed ventricular fibrillation at a mean rectal temperature of 15 6 ± 1 96°C This reduction in the frequency of fibrillation was not significant at the 0 05 level

The second group of dogs consisted of 8 animals treated with continuous intravenous infusion of 1 I U per kilogram per minute of oxytocin The infusion was initiated at a rectal temperature of 25°C and continued during the remainder of the experimental period Two of 8 dogs (25

Table II Effect of various concentrations of oxytocin on the diastolic threshold contractility conduction velocity and absolute refractory period of the isolated cat papillary muscle

Oxytocin concentration (mU /ml)	Diastolic threshold (volts)		Amplitude of contraction (mm)		Conduction velocity (mm /sec)		Refractory period (msec)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
0	2 1 ± 0 5	2 7 ± 1 4	10 4 ± 0 06	12 2 ± 0 16	229 ± 15	212 ± 9 6	196 ± 9 3	196 ± 9 3
5	1 2 ± 0 11	1 4 ± 0 12	9 0 ± 0 11	9 8 ± 0 12	238 ± 11.8	218 ± 15 8	210 + 4 5	208 ± 3 7
10	1 3 ± 0 19	1 3 ± 0 17	11 2 ± 0 03	12 0 ± 0 07	200 ± 15 2	181 ± 29 6	203 ± 3 7	220 ± 3 2
15	1 3 ± 0 06	1 8 ± 0 28	10 4 ± 0 13	13 6 ± 0 11	272 ± 9 6	273 ± 19 3	214 ± 5 3	274 ± 2 5
30	1 3 ± 0 11	1 72 ± 0 13	9 8 ± 0 04	13 0 ± 0 04	232 ± 7 9	237 ± 8.5	216 ± 2 5	274 ± 2 5

*Significant at the 01 level (Student test

Each figure represents the mean ± standard error of five experiments before (Pre) and after (Post) 120 minutes of exposure to oxytocin

Table III Effect of oxytocin on the incidence of ventricular fibrillation and terminal rectal temperature in dogs subjected to acute hypothermia

Category	*Number of dogs*	*Incidence of ventricular fibrillation*	*Terminal rectal temperature (° C.) (± S. E.)*
Control	12	10 (83%)	19.2 ± 5 8
Oxytocin (2 I.U./Kg./30 min.)	7	3 (43%)	15.6 ± 1.96†
Oxytocin (15 I.U./Kg./min.)	8	2 (25%)	14.9 ± 1.63†

*Significant at the .05 level (chi square test)
†Significant at the 0.01 level (Student t test)

per cent) in this group succumbed to ventricular fibrillation at a mean rectal temperature of 14.9 ± 1.63°C. This represents a significant reduction in the incidence of ventricular fibrillation as compared with the control group (p = <0.05). Moreover, the temperature to which the animals cooled before cardiac arrest occurred was reduced significantly in the oxytocin-treated group (p = <0.01) (Table III). No difference in mean heart rate or QRS duration existed between the control and oxytocin treated groups during the entire cooling period. Immediately after the start of the infusion of oxytocin the mean arterial pressure did show a transient increase of 10 to 20 mm. Hg. However, 5 to 20 minutes after the start of the infusion of oxytocin the blood pressure had returned to a level which was not different from the mean blood pressure of the control animals.

Discussion

Oxytocin has proved to be effective in the prevention or the treatment of cardiac arrhythmias produced by the administration of cyclopropane-epinephrine, the administration of chloroform-epinephrine, electrical stimulation,[3] injection of picrotoxin into the lateral ventricles, and in this study, the acute reduction of body temperature. To date, only ventricular fibrillation produced by toxic doses of ouabain has been resistant to oxytocin therapy.[3] It has been suggested that oxytocin exerts a quinidine-like action which is the basis for its antiarrhythmic activity.[3] However, a comparison of the effects of quinidine and oxytocin on the electrophysiologic properties of cardiac muscle indicates that oxytocin cannot be classified as a quinidine-like agent in the strict sense. Quinidine is known to raise the threshold, prolong the refractory period, and decrease the conduction velocity of the ventricle.[3] The elevation of the ventricular threshold *is probably the main factor responsible* for the antiarrhythmic activity of quinidine, since this agent has been shown to be more effective against mechanically induced arrhythmias than against arrhythmias due to disturbances in the refractory period or conduction velocity.[1] On the other hand, in this study, oxytocin was found to prolong the refractory period without producing any change in the threshold or conduction velocity of the papillary muscle. The prolongation of the refractory period probably is responsible for the antiarrhythmic effect of oxytocin in hypothermia, at least. For it has been shown that ventricular fibrillation in hypothermia is related to a disproportionate change in the conduction velocity and refractory period at low body temperatures, so that the decrease in conduction velocity is not matched by a proportional increase in the refractory period. Thus, agents which selectively increase the conduction velocity or prolong the refractory period should be effective antifibrillary agents in hypothermia. In this regard, norepinephrine and mephentermine,[6] which increase conduction velocity, and oxytocin and N,N bis (phenyl-carbamoyl methyl) dimethyl ammonium chloride,[7] which prolong the refractory period, can reduce significantly the incidence of ventricular fibrillation in hypothermia.

It is not certain whether the prolongation of the refractory period by oxytocin can account for its protective action against experimental arrhythmias other than those which develop during hypothermia. In the case of oxytocin's protective action against atrial or ventricular fibrillation induced by electrical stimulation, prolongation of refractoriness could abolish this arrhythmia, since evidence does exist that electrical stimulation induces a re-entry type of arrhythmia.[12] As for the arrhythmias in

duced by cyclopropane or chloroform-epinephrine these cardiac disturbances appear to be dependent on blood pressure, i.e., an elevation in systolic pressure is required to initiate the arrhythmia.[13] Although oxytocin caused a rise in blood pressure in the hypothermic dog oxytocin in normothermia has been reported to produce hypotension by a peripheral vasodilator action.[1] This fall in pressure may be responsible for its effect in arrhythmias induced by cyclopropane or chloroform epinephrine, although the direct action of oxytocin on the heart cannot be ruled out as a contributing factor. Arrhythmias induced by pentylenetetrazol and picrotoxin apparently are related to an increased sympathetic and parasympathetic outflow from the central nervous system.[15,1] Whether the antiarrhythmic effect of oxytocin in these experimental situations is related to its direct effect on the refractory period of the heart or to an inhibition of activity of the autonomic nervous system is not known. The failure of oxytocin to prevent ouabain-induced fibrillation may be the result of inadequate amounts of oxytocin employed. Varma and Melville[4] failed to observe any protective effect with 0.25 to 0.50 I.U. per kilogram per minute. In our hypothermic studies, a minimum of 1 I.U. per kilogram per minute intravenously was required to demonstrate significant antifibrillary activity.

Summary

The direct effect of synthetic oxytocin (Syntocinon) on cardiac tissue was studied in isolated atria and isolated papillary muscle preparations. No change in atrial rate or amplitude of contraction was noted until the oxytocin concentration was increased to 90 milliunits per milliliter. At this concentration a significant decrease in atrial rate occurred. In the papillary muscle preparation the amplitude of contraction increased significantly at a concentration of 15 milliunits per milliliter of oxytocin. The only other change produced by oxytocin was a prolongation of the refractory period without a concomitant reduction in conduction velocity.

On the basis of the oxytocin effect on the ventricular refractory period the potential antiarrhythmic activity of oxytocin was studied in hypothermia. A dose of 1 I.U. per kilogram per minute of oxytocin significantly reduced the incidence of ventricular fibrillation in hypothermic dogs from 83 to 25 per cent. The data suggest that the antiarrhythmic activity of oxytocin may be a function of its ability to prolong the refractory period of cardiac muscle without causing a concomitant reduction in conduction velocity.

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Correlation of right ventricular pressure with right ventricular weight

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A number of studies have established normal weight relationships[1-4] of the right and left ventricles, as well as the effects of disease on the relative preponderance of one or the other.[5-12] In addition, changes in the relative weights of the ventricles during fetal and neonatal development have been shown.[13, 4] Recent studies in cattle have indicated that there is a correlation between increased right ventricular weight and pulmonary hypertension.[1, 22] This study in the newborn puppy was undertaken to determine the correlation between right ventricular pressure and right ventricular weight during early neonatal life when the hemodynamics are changing rapidly.[23,4]

Methods

Seventy-eight mongrel puppies ranging in age from 1 day to 4 weeks were studied. Thirty-five of these were subjected to catheterization of the right side of the heart. An external jugular vein was exposed under local anesthesia, and a PE-60 tubing was passed into the right ventricle. In some of the older animals it was possible to enter the pulmonary artery, using a No. 4 Lehman catheter. Pressures were obtained by means of a P23D Statham transducer energized with a Hathaway carrier-amplifier system and were recorded photographically with a Honeywell oscillograph. All animals were autopsied. No cardiovascular anomalies were present. The total ventricular weight was determined after removing the great vessels, atria, fat, and valves from each heart. The free wall of the right ventricle was dissected from the left ventricle and septum along its line of attachment; the septum was not divided. The papillary muscles attached to the right side of the septum were removed with the right ventricle. The free wall of the right ventricle was then weighed on a scale accurate to 0.01 grams and calculated as a per cent of the total ventricular weight (RV/T × 100).

In addition, RV/T values were established in a series of 35 healthy adult mongrel dogs. All animals in these studies were born and raised at approximately 5,000 feet altitude. Recent work has shown that RV/T is dependent on altitude.[25]

Results (Table I)

During the first week of life, right ventricular pressures fell rapidly to adult

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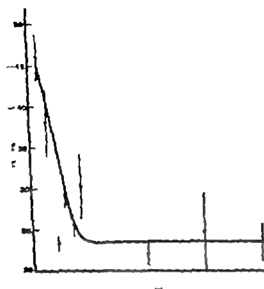


Fig. 1 The right ventricular peak systolic pressure is plotted against the age of the animal in weeks. Each vertical black bar represents one standard deviation.

levels. (Fig 1) Values of RV T also followed a similar and rapid fall to adult levels (Fig 2) There was an excellent correlation between right ventricular pressure and RV T (Fig 3) The results suggest that the RV T relationship is a sensitive indicator of the pressure in the right ventricle and if no outflow obstruction is present in the pulmonary artery as well Although both right ventricular pressures and RV T values fell rapidly to normal adult levels there was a definite but small lag in the decline of RV T as compared to the fall in pressure (Fig 3)

Discussion

Rudolph and associates[20] and Phillips and associates have reported that the pulmonary arterial pressure in newborn puppies reached adult levels by 1 week of life. Our studies on pressure are in agreement with their findings. Furthermore the present investigation has shown that RV T accurately reflects the changing pulmonary arterial pressure since it too reaches the adult level at approximately 1 week of age.

This is in contrast to the rate of change in the histologic appearance of the pulmonary arteries. Thus, Phillips and associates[21] have shown that the pulmonary arteries in puppies maintain their fetal characteristics for at least 1 month—considerably longer than the time required for the pulmonary arterial pressure and

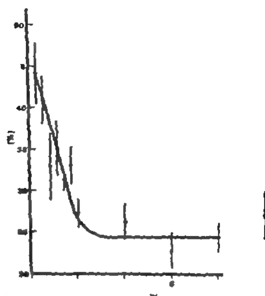


Fig 2 The weight of the free wall of the right ventricle in relation to the total ventricular weight (RV/T × 100) is plotted against the age of the animal in weeks. Each vertical bar represents one standard deviation.

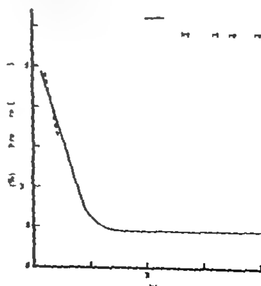


Fig. 3. The RV/T and right ventricular peak systolic pressure (right heart pressure) are plotted together in relation to the age of the animal in weeks. Note that the pressures fall toward normal slightly faster than do the RV/T values.

Table I

RV/T				Right ventricular systolic pressure		
Age in days	*Number of animals*	*Average RV/T (%)*	*One standard deviation*	*Number of animals*	*Average pressure (mm. Hg)*	*One standard deviation*
1	21	44.2	3.7	4	46	2.8
2	10	41.0	2.9	4	38	4.0
3	7	33.0	4.0	5	23	0.9
4	8	35.2	3.3	4	29	1.5
5	3	31.3	1.3	4	26	1.3
6	4	33.1	2.2	4	30	3.9
7	3	27.3	1.7	1	30	
14	9	26.2	2.2	2	22	1.4
21	4	22.7	2.2	3	[illegible]	4.6
28	3	24.4	1.7	4	23	2.3
Adult	35	27.0	2.8			

RV/T to decrease to adult levels. In addition Rudolph and associates[22] have shown a significant decrease in right ventricular pressure when acetylcholine was given to puppies *prior* to 1 week of life. Their findings suggest that an increased vascular tone is responsible for the high pressures observed during the first days after birth. The nature of the stimulus which is responsible for this vasoconstriction in the newborn puppy is unknown.

A significant correlation between RV/T and right ventricular pressure has been demonstrated during the rapidly changing neonatal period. Whether this can be applied to the relatively stable hemodynamic findings in adults at the time of postmortem examination remains to be determined. Possibly such information could be obtained by a systematic study *relating* pathologic changes to precise physiologic data obtained during antemortem studies.[23]

Summary

The weight of the right ventricle expressed as a per cent of the total myocardial weight (RV/T × 100) was related to right ventricular pressure in the neonatal puppy. It was shown that during the first 4 weeks of life the regression curves of the right ventricular pressure and RV/T were strikingly similar, thus establishing this quantitative postmortem measurement as a sensitive indicator of right ventricular pressure.

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The systemic and coronary hemodynamic effects of diazoxide

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The hemodynamic and especially the hypotensive[1] effects of chlorothiazide have been extensively investigated. Acute studies have shown a decrease in cardiac output[2-4] and left ventricular work with reduced central venous pressure but without a significant decrease in coronary blood flow.[4] Plasma volume is reduced, apparently secondary to the loss of sodium and water. Furthermore, it has been shown that the hypotensive response is reduced by the administration of sodium chloride[4] and augmented by the restriction of sodium. Infusion of dextran to restore the circulating blood volume is reported to correct the reduced cardiac output and increased peripheral resistance which are produced by chlorothiazide. Hence it has been tempting to assume that the hemodynamic response is produced by the changes in water and electrolytes. On more prolonged administration, however, cardiac output tends to return to normal, as does plasma volume and total body sodium,[1] and yet at this time the blood pressure and vascular resistance remain lower than control values. When these facts are coupled with the observation that the acute hemodynamic changes probably occur before there is time for fluid and electrolyte readjustment to take place,[4] it may be appreciated why the hemodynamic effects of chlorothiazide

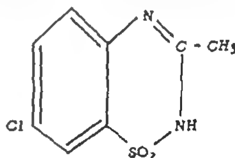


Fig. 1. Diazoxide.

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have not been elucidated to the satisfaction of all.

In general, it seems to have been assumed that the hemodynamic effects of all of the benzothiadiazine group are the same as those of chlorothiazide,[11] although there seems to be a dearth of hemodynamic data on this point. It was of considerable interest, therefore, when a benzothiadiazine derivative, diazoxide (SRG 95213, Fig. 1), was produced, for this compound seemed to separate the antihypertensive and diuretic activity of the benzothiadiazine compounds, preserving only the hypotensive effects.[11] The present report concerns the hemodynamic effects of diazoxide in intact anesthetized mongrel dogs and in man.

Material and methods

The study was done in two parts. The first was the investigation of the hemodynamic effects of diazoxide in intact anesthetized experimental animals, and the second was the determination of the acute hemodynamic effects of its administration to unanesthetized man.

Ten mongrel dogs which weighed between 16 and 31 kilograms (average 21.5 kilograms) were anesthetized with 3 mg. per kilogram of morphine sulfate subcutaneously, followed in 1 hour by the intravenous administration of 0.25 mg. per kilogram of body weight of a 50:50 mixture of Dial urethane and veterinary pentobarbital.* When anesthesia was obtained, cardiac catheters were maneuvered fluoroscopically into the right atrium, coronary sinus, and the pulmonary artery, and Cournand needles were placed percutaneously in both femoral arteries. Cardiac output was determined by the direct Fick principle with collection of expired air in a Tissot spirometer via a cuffed endotracheal tube. Gas analyses for oxygen and carbon dioxide were made on the specimens of blood by the Van Slyke-Neill method and on specimens of air with the Scholander apparatus. Analyses for nitrous oxide in the blood were made by the method of Orcutt and Waters. Coronary blood flow was determined by the nitrous-oxide saturation method utilizing a partition coefficient of 1 between blood and myocardium. Pressures were recorded via Statham strain gauges with the mean pressure determined by electrical integration on the Gilson macropolygraph. Standard formulas were used for all calculations. In the calculation of cardiac work, neither right nor left atrial pressure was subtracted from the appropriate arterial pressure, since the left atrial pressure was not determined and the amount of error introduced by failure to subtract such pressures is relatively small. Cardiac output was also determined by an indicator-dilution method utilizing indocyanine green and a cuvette densitometer. Calibrations for the indicator-dilution curves were made in each case utilizing blood of the dog under study. In each animal, after a control determination of cardiac output and coronary blood flow, 5 mg. per kilogram of diazoxide was given rapidly, usually through the coronary sinus catheter. Approximately 10 minutes later a second determination of cardiac output and coronary blood flow was made. The control and experimental observations were compared for each parameter using the t test.

Similar studies were performed in 8 anesthetized dogs pretreated with 0.1 to 0.3 mg. per kilogram of reserpine intramuscularly over a period of 1 to 3 days prior to study in order to deplete catecholamines. In these animals diazoxide was given more slowly in order to avoid excessive hypotension. Furthermore, an attempt was made to determine cardiac output and coronary blood flow in 5 dogs which were pretreated 2 hours before the study with a dose of approximately 25 mg. per kilogram of chlorothiazide intravenously. In only 3 of these dogs were studies repeated after diazoxide, because of an adverse response to the drug. The data on coronary flow from one of these 3 animals were discarded because the nitrous-oxide curves gave evidence that the coronary sinus blood was contaminated and hence the coronary flow data were vitiated. In 7 animals, cardiac output was determined serially during the control observations, during the acute response

*Dial urethane, furnished through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J., contains Dial, 100 mg./ml., monoethylurea, 400 mg./ml., and urethane, 400 mg./ml. Veterinary pentobarbital contains 60 mg./ml. of sodium pentobarbital.

after diazoxide and again during the second determination of cardiac output and coronary blood flow In 2 animals the effect of diazoxide was studied about 1 hour after an intravenous dose of 5 mg per kilogram of dichloroisoproterenol In 2 animals, during the recovery phase after acute administration of diazoxide the response of the arterial pressure was measured during rapid intravenous administration of 5 mg of phentolamine.

Studies in human beings were made in 5 fasting unanesthetized subjects who had received no premedication. The first subject was given 100 mg of diazoxide over a period of 5 minutes into the coronary sinus however there was relatively little hemodynamic effect. In the other 4 subjects a dose of 3 mg per kilogram was given over a period of 5 minutes. The dose was given in increments so that although the entire dose was not given at once one fifth of the dose was given rapidly each minute In the human subject, two cardiac catheters were utilized one of which was manipulated into the pulmonary artery and the other into the coronary sinus. The systemic arterial blood pressure was recorded and specimens of systemic arterial blood were drawn through an indwelling Cournand needle in the femoral artery Chemical analyses and calculations were made in the same fashion as has been described for the experimental animals.

Results

In 2 from the series of 25 dogs, administration of diazoxide precipitated sudden death One of these dogs had been pretreated with chlorothiazide and the other had not In both of these animals when the heart was exposed ventricular fibrillation was found and is presumed to have been the mechanism of death In a third dog which had been pretreated with chlorothiazide paroxysmal supraventricular tachycardia with marked hypotension began very shortly after the administration of diazoxide After the arrhythmia had been observed for some time an attempt was made to interrupt it with an electrical shock from an alternating-current external defibrillator but ventricular fibrillation was precipitated In both cases in which the effort was made the heart was revived successfully by massage countershock, and epinephrine In a fourth dog pretreated with dichloroisoproterenol a supraventricular tachycardia occurred but subsided after several minutes without treatment

It was observed that if the drug was given rapidly rather marked systemic arterial hypotension occurred very quickly accompanied by a transient increase in right atrial and pulmonary arterial pressure The most marked systemic hypotension tended to be transient but significantly lower blood pressure remained throughout the subsequent hour of study and observation. If diazoxide was given slowly however the animals developed considerable tachycardia with an increase in cardiac output and a decrease in vascular resistances but without as much decrease in blood pressure. During this state the sudden intravenous injection of 5 mg per kilogram of diazoxide produced a hypotensive response similar to that produced by a single sudden injection During the recovery phase after the acute hypotensive response to diazoxide the sudden administration of phentolamine produced an acute transient decrease in systemic arterial pressure (see Fig 2)

The results of the hemodynamic study in dogs as determined by the indicator-dilution method are presented in Fig 3 and reveal the acute increase in cardiac output and decrease in total peripheral resistance All dogs but one (No 5) showed a similar response and no explanation is offered for this discrepancy The mean circulation time as determined from the indicator-dilution curves decreased significantly Table I contains the data calculated by the Fick principle and the nitrous-oxide method and shows that during the experimental study approximately 10 through 25 minutes after the administration of diazoxide there was an increase in cardiac rate which was accompanied by a decrease in mean pressure in the systemic and pulmonary arteries as well as in the right atrium The minute volume of respiration increased slightly but not significantly and was accompanied by a significant increase in respiratory rate Body oxygen consumption was unchanged as was the carbon-dioxide excretion and consequently the respiratory quotient was

unaltered The arterial oxygen content remained unchanged but the venous oxygen content rose, with significant narrowing of the arteriovenous oxygen difference Similarly the coronary sinus oxygen content increased significantly with considerable narrowing of the arterial-coronary sinus oxygen difference. Apparently associated with the increase in ventilation was a decrease in the arterial and mixed venous carbon-dioxide content, accompanied by narrowing of the venoarterial carbon-dioxide difference. The coronary sinus blood carbon-dioxide content also decreased significantly with considerable narrowing of the coronary sinus-arterial carbon-dioxide difference. The femoral arterial pH rose slightly but not significantly whereas the arterial hemoglobin and hematocrit were unchanged. The cardiac output increased significantly Left and right ventricular work was slightly but not significantly increased Both total peripheral and total pulmonary resistance were significantly reduced. Coronary blood flow was markedly increased accompanied by a significant increase in myocardial oxygen consumption whereas the cardiac respiratory quotient decreased and coronary vascular resistance was significantly reduced The calculated index of efficiency which relates left ventricular work to left ventricular oxygen usage did not change significantly There were consistent increases in the ratio of coronary blood flow to left ventricular work ($p < 0.01$) to left ventricular oxygen con



Fig 2. The acute response to phentolamine during the recovery phase after the administration of diazoxide

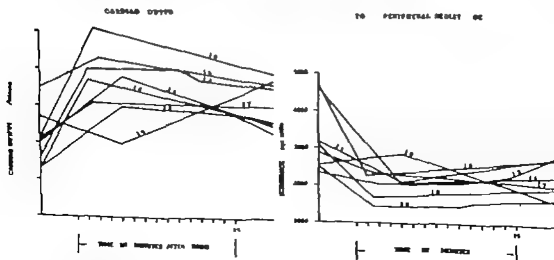


Fig. 3. The acute systemic hemodynamic response to intravenous administration of diazoxide as determined utilizing indicator-dilution curves for measuring cardiac output.

Table I. Systemic and coronary hemodynamic effects of diazoxide in anesthetized intact dog

Parameter	Control	Study	SEM d.f.	% Change	p value <
Heart rate (beats/min.)	83	124	5.387	+49.4	0.001
Mean arterial blood pressure (mm. Hg)	118	111	2.224	−5.9	0.1
Mean pulmonary arterial blood pressure (mm. Hg)	14	12	3.252	−14.3	0.01
Oxygen consumption (ml./min.)	111	112	0.284	+0.91	0.8
Mean right atrial blood pressure (mm. Hg)	2.1	1.2	2.[illegible]	−42.9	0.05
Body respiratory quotient	0.8	0.80	1.071	−3.7	0.4
Arterial oxygen content (ml./100 ml. of blood)	17.3	17.3	0	0	0
Arteriovenous oxygen difference (ml./100 ml. of blood)	3.5	2.7	6.618	−22.9	0.001
Coronary sinus oxygen content (ml./100 ml. of blood)	6.5	11.9	7.638	+83.1	0.001
Mixed venous CO_2 content (ml./100 ml. of blood)	52.9	49.6	11.786	−6.2	0.001
Arterial hematocrit (%)	41	40	1.223	−2.2	0.3
Cardiac output (L./min.)	3.3	4.3	2.907	+30.3	0.02
Left ventricular work (Kg. M./min.)	5.4	6.5	1.783	+20.4	0.2
Right ventricular work (Kg. M./min.)	0.6	0.7	1.053	+16.7	0.4
Total peripheral resistance (units)	3,180	2,142	3.923	−32.6	0.01
Total pulmonary resistance (units)	379	234	4.091	−38.3	0.01
Coronary blood flow (ml./100 Gm./min.)	100	356	3.953	+255	0.01
Left ventricular oxygen usage (ml./100 Gm./min.)	[illegible].2	15.6	4.481	+52.9	0.01
Cardiac respiratory quotient	0.83	0.77	3.333	−9.41	0.01
Coronary vascular resistance (units)	1.22	0.41	11.250	−66.4	0.001
Index of efficiency (LVW ÷ LV O_2 usage)	0.52	0.43	1.500	−17.3	0.2

Standard error ... the mean difference.

Table II. Systemic and coronary hemodynamic effects of diazoxide in man

Study number	Stud.	Weight (Kg.) Dose (mg.)	Heart rate	Mean arterial BP (mm. Hg)	Mean pulmonary arterial BP (mm. Hg)	Oxygen consumption (c.c./min.)	Respiratory quotient	Δ Arteriovenous oxygen	Coronary sinus oxygen (ml./100 ml. of blood)	Δ Arterial coronary sinus oxygen (ml./100 ml. of blood)	Cardiac R.Q.
1	C	80	[illegible]	103	17	310	0.77	3.8	7.4	11.0	0.75
	S	100	84	105	1	312	0.77	3.8	8.5	9.4	0.78
–	C	71	73	95	16	28[illegible]	0.68	3.9	7.4	11.7	0.75
	S	213	83	93	15	284	0.70	3.0	10.3	9.1	0.74
3	C	91	85	116	18	304	0.85	5.3	7.3	13.2	0.76
	S	2[illegible]3	99	93	18	299	0.74	4.4	10.3	10.7	0.69
4	C	81	81	115	18	279	0.82	3.5	6.5	12.3	0.88
	S	243	86	110	[illegible]	268	0.78	3.3	9.7	9.4	0.8
[illegible]	C	93	80	89	13	286	0.65	3.3	4.2	13.8	0.[illegible]3
	S	[illegible]46	81	87	12	325	0.61	3.4	7.5	10.2	0.85
Average control			80	104	16	289	0.75	4.0	6.4	12.8	0.[illegible]8
Average study			85	96	16	[illegible]99	0.71	3.5	9.5	9.9	0.78

Stud. 1 ... included in averages.

sumption ($p < 0.001$) and to cardiac rate ($p < 0.01$)

The results in the 8 animals pretreated with reserpine may not be strictly comparable to the results in the nonreserpinized animals, since the anesthetic dose was reduced because of the sedation from reserpine. Furthermore the diazoxide has to be given more slowly because of the more profound hypotensive response to its administration. Indeed one dog had to be discarded because of a "shocklike state after the intravenous administration of diazoxide. The dogs which had received less reserpine and which had been treated 24 and 48 hours showed a pattern of hemodynamic response similar to that in the nonpretreated animals with decreased total peripheral pulmonary and coronary resistance Simultaneously there was narrowing of the arteriovenous oxygen differences across the systemic and coronary vascular beds and increased cardiac output and coronary blood flow Coronary blood flow increased in each of the 4 animals in which the heart rate increased Those animals which had been pretreated for 72 hours and which had received the larger doses of reserpine tended not to increase their cardiac rate cardiac output or coronary blood flow to the same degree as did the controls or those which had been pretreated for the shorter period Myocardial oxygen consumption in the dogs treated with reserpine for 72 hours tended not to increase as it did in those pretreated for only 48 hours or in the control animals.

The data in the animals pretreated with chlorothiazide are not basically different from those in the control dogs since cardiac output and coronary flow increased and the systemic pulmonary and coronary resistance decreased The dogs pretreated with dichloroisoproterenol had high control values for cardiac rate cardiac output and coronary blood flow Subsequent to the administration of diazoxide however they showed a response similar to that of the control animals with decreased systemic pulmonary and coronary resistance accompanied by increased oxygen content in the

Cardiac index (L/min/M)	Total peripheral resistance (g.s ads)	Total pulmonary resistance	Left ventricular work I (Kg.M/min/M)	Right ventricular work I	Coronary blood flow (ml/100 Gm/min)	Left ventricular oxygen usage (/100 Gm/m)	Coronary vascular resistance (units)	Arterial hematocrit ( )	Ind of ficiency (LVW + LV O₂ usage)
4 1	1 009	167	5 8	1 0	118	13 0	0 87	45	0 45
4 1	1 022	165	5 9	1 0	139	13 1	0 76	45	0 45
4 0	1 032	174	5 2	0 9	170	14 0	0 79	41	0 37
5 1	785	127	6 5	1 0	142	12 9	0 63	43	0 50
2 7	1 616	251	4 3	0 7	74	9 8	1 57	47	0 44
3 2	1 097	212	4 1	0 8	90	9 6	1 03	47	0 43
4 1	1 133	180	6 4	1 0	103	12 7	1 12	47	0 50
4 5	1 007	183	6 7	1 2	127	11 9	0 87	47	0 56
4 0	821	120	4 8	0 7	55	7 6	1 62	44	0 63
4 4	727	100	5 2	0 7	77	7 9	1 13	43	0 66
3 7	1 156	181	3 2	0 8	83	11 0	1 28	45	0 49
4 3	904	156	5 6	0 9	109	10 6	0 9	45	0 54

coronary sinus blood and increased coronary blood flow

The data for the human subjects who were given diazoxide are presented in Table II The subject who received 100 mg of diazoxide had essentially no hemodynamic changes. Those who received the larger dose of 3 mg per kilogram however showed a consistent increase in cardiac rate accompanied by a decrease in mean systemic arterial blood pressure but no significant change in the pulmonary arterial pressure The arterial oxygen content remained stable whereas mixed venous oxygen content increased with narrowing of the arteriovenous oxygen difference The coronary sinus oxygen content increased consistently in all cases, with narrowing of the arterial coronary sinus oxygen difference. Arterial hemoglobin and hematocrit as well as femoral arterial and coronary sinus pH showed no consistent trend The cardiac index increased and the calculated total peripheral resistance decreased in all cases, whereas left ventricular work was variable but essentially unchanged although the right ventricular work increased in 3 of 4 subjects, including the one who received the 100-mg dose Myocardial oxygen consumption was variable decreasing slightly in 3 of 4 subjects, whereas the coronary vascular resistance decreased in all The calculated cardiac efficiency was not remarkably altered

Discussion

The data reveal a reasonably consistent pattern in experimental animals and man Diazoxide appears to be chiefly a vasodilator acting not only on the peripheral vessels but also on the coronary circulation Although a decrease in total pulmonary resistance occurs simultaneously since neither pulmonary wedge nor left atrial pressures were measured the data justify no conclusions concerning changes in the size of the lumen of the pulmonary vessels. It seems reasonable to presume however that the pulmonary vessels were affected similarly to the systemic and coronary vessels. Furthermore direct experiments with measurement of blood flow by a rotameter in the femoral, renal and coronary arteries after intra arterial injection of diazoxide have shown increased flow After intravenous administration of diazoxide direct measurements showed that coronary blood flow was generally increased [1] In vitro experiments on strips of smooth muscle from rabbit aorta have indicated that diazoxide antagonized aortic contraction induced by norepinephrine, angiotensin and serotonin [11] It seems doubtful however that much of the effect of the agent is due to antagonism of catecholamines, since the hypotensive response tends to be more pronounced in reserpine pretreated i.e. catecholamine-depleted animals. Furthermore the response to the drug after dichloroisoproterenol in a dose of 5 mg per kilogram is not remarkably different from that in control animals. The fact that myocardial oxygen consumption and coronary blood flow failed to increase to the same degree after diazoxide in animals pretreated with reserpine for 72 hours is compatible with the release of catecholamines during the hypotensive phase of the drug's action as is the response to phentolamine and the fact that the reserpinized animals tended to become more hypotensive or even to go into shock.

Whereas at least a part of the increase in coronary blood flow may be related to the increase in cardiac rate it cannot be explained entirely in this manner since coronary blood flow increased more percentagewise than did cardiac rate. Similarly coronary flow increased more than did left ventricular work or myocardial oxygen consumption The fact that the coronary sinus blood oxygen content increased supports the hypothesis that the increase in coronary blood flow cannot be attributed purely to an increased metabolic demand by the heart These data as well as those from direct perfusion of the coronary vessels during measurement of blood flow by a rotameter are consistent with an increase in the cross-sectional area of the coronary vessels, thereby reducing resistance to flow

A comparison of the acute hemodynamic effects of diazoxide with those of chlorothiazide indicate rather marked differences. Immediately subsequent to the administration of chlorothiazide total peripheral resistance increased accompanied by no real change in coronary vascular resistance or coronary blood flow whereas cardiac output was significantly reduced [4] Further

more, in the present studies the hemodynamic effects of diazoxide were similar in control animals and in those which had been pretreated 2 hours before with 25 mg per kilogram of chlorothiazide. Long term studies of the action of chlorothiazide indicate that after the acute reduction in cardiac output, readjustment takes place, with an increase in cardiac output toward normal and a reduction in peripheral vascular resistance. During this phase plasma volume was found to return to normal whereas total body water remained low. These peripheral vasodilating effects of chlorothiazide have not been explained to the complete satisfaction of most investigators although a direct action on vascular smooth muscle was suggested from animal experiments.[13] Thus, the hemodynamic effects of chlorothiazide after more prolonged administration become more similar to but not so pronounced as the vasodilator response obtained immediately on administration of diazoxide.

Summary

1 Hemodynamic studies including the determination of cardiac output and coronary blood flow have been made before and after the intravenous administration of diazoxide to anesthetized intact dogs and unanesthetized man. The response was essentially the same in the dog and in man.

2. Administration of this agent intravenously was accompanied by an acute reduction in peripheral total pulmonary and coronary resistances, with a decrease in systemic and pulmonary arterial pressures and an increase in cardiac output and coronary blood flow.

3 Coronary sinus oxygen *content* increased with the per cent increase in coronary blood flow significantly greater than the change in cardiac rate left ventricular work, and left ventricular oxygen consumption.

4 The acute hemodynamic effects of diazoxide in control animals are not significantly different from the effects in animals pretreated with chlorothiazide or small doses of reserpine.

5 Although both diazoxide and chlorothiazide are benzothiadiazine derivatives their acute hemodynamic effects differ greatly

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The significance of the rate and output related variations in the A_2-OS interval

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The increasing efficacy of mitral valve surgery has rapidly expanded the group of patients who have been subjected to surgery or who are considered for surgery. Studies performed for diagnostic purposes and for postoperative evaluation have given us an opportunity to evaluate certain clinical observations. We have attempted to explain the change or lack of change in A_2-OS (aortic second sound to opening snap) and Q-M_1 (onset of QRS to mitral first sound) intervals in certain mitral lesions.

Method

A phonocardiograph amplifier designed and constructed by Mr. Thomas G. Arnold, Jr. has been previously described. Paper speeds of 75 and 110 mm. per second were used; recording was photographic. Two or three sound channels, the arterial wave form, and the electrocardiogram were recorded simultaneously in order to permit identification and timing of components. The filters usually employed were comparable to high-frequency or logarithmic filters. They exceed the upper range of some commercially available apparatus. Measurements were made with the subjects at rest and after moderate supine exercise.† A_2-OS and Q-M_1 intervals were estimated to 0.001 second but with a presumed accuracy of 0.003 second (see Fig. 4). Intervals were obtained for a rate range covering as completely as possible 60 to 100 beats per minute. Most recordings were made in held expiration although phasic variations were usually small. Both intervals were recorded from the same cycle. An occasional Q-M_1 interval could not be determined with accuracy and slope lines for the A_2-OS intervals were drawn from an average of 14 points, whereas lines for Q-M_1 intervals were drawn from an average of 11 points. An average A_2-OS interval plot against the R-R interval of the preceding cycle is shown in Fig. 1. Wells index was computed as suggested.[2] The per cent change in A_2-OS interval was computed as follows:

$$\frac{A_2\text{-OS}\ (60) - A_2\text{-OS}\ (100)}{A_2\text{-OS}\ (100)} \times 100$$

Records in which the variation in rate with exercise was not sufficient to permit an accurate establishment of slope were either repeated or discarded.

Results

The records of 22 patients who were subjected to surgery, catheterization of the left side of the heart, autopsy, or a combination of these are considered. Table I summarizes the pertinent findings.‡

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†Three patients (M.P., M.S., and E.B.) in atrial fibrillation were retrospectively included in the study. They had sufficient variation in the diastolic filling period to cover the desired rate range. They were not exercised.

‡Seventeen of these patients are included in a left-heart study group which is being followed by the Department of Clinical Physiology of Vanderbilt University Hospital.

There were 5 patients with tight mitral stenosis as the single hemodynamically significant lesion. The change in A_2-OS interval over the selected rate range varied from 50 to 93 per cent. The patient who showed the most marked variation was a moderately symptomatic 16-year-old girl with excellent cardiac reserve and minimal pulmonary vascular changes. In 4 of the 5 patients the Wells index indicated a significant mitral gradient. In Patient M.P. who had the severest lesion of this series, the Wells index was −1 (Fig. 2).

There were 5 patients with a moderate degree of mitral stenosis and minimal or no regurgitation. Three of these deserve special attention. Patient J.M. had an A_2-OS reduction of only 23 per cent and a Wells index of −2. Her symptoms had been abrupt in onset accompanied by failure and atrial fibrillation and relieved by digitalis and reversion to sinus rhythm. The C reactive protein was 0 and the antistreptolysin titer was 166 units. At operation, the mitral valve area was 2.0 sq. cm.; there were active Aschoff bodies in the atrial appendage. The patient, who was pregnant at the time of operation, has continued to be symptomatic on digitalis since the operation despite an excellent mechanical split of the valve without significant regurgitation. She has required careful management during the course of her pregnancy in order to control her congestive failure. Since her mean left atrial pressure was only 12 mm. Hg prior to operation the primary problem was suspected to be an active rheumatic process.

Table I. Variation in A_2-OS interval and its comparison with clinical information and the Wells index

Patient	A_2-OS (60)	A_2-OS (100)	% Change	Q-M (60)	Q-M (100)	Catheterization		Surgery	
						Wells index	MVA* cm.	MVA cm.	Insufficiency
B.S.	0.077	0.040	93	0.076	0.087	2		3	0
W.K.	0.080	0.044	82	0.084	0.095	3	7	[illegible]	0
J.L.	0.063	0.038	66	0.076	0.096	3	6	4	0
M.W.	0.056	0.037	50	0.079	0.089	4	6	"Little finger	Minimal
M.P.	0.112	0.066	70	0.063	0.076	−1		4 × 6 mm. port	–
W.B.	0.129	0.064	100	0.061	0.088	−1	1.5	Index finger	0
P.W.	0.063	0.033	91	0.090	0.090	5	1.3	Index finger	0
M.S.	0.090	0.057	58	0.065	0.078	0		1.4	0
J.D.	0.070	0.044	60	0.079	0.091	3		1.0	0
J.M.	0.107	0.080	23	0.064	0.079	−2	1.9	2.0	0
W.C.	0.074	0.056	32	0.082	0.106	3	2.1†		¼ FF
O.H.	0.090	0.073	23	0.086	0.090	1	2.2†		½ FF
E.R.	0.076	0.062	21	0.081	0.098	2		Tip of index finger	Moderate regurgitant jet
L.A.	0.107	0.080	33	0.08	0.08	−1	3.0+†		1 – FF
J.C.	0.097	0.075	30	0.070	0.087	−1		3.0	Moderate jet
M.C.	0.120	0.104	15	0.063	0.088	−3	3.0†		1 – FF
M.G.	0.103	0.081	27	0.068	0.068	0	3.0+†		I – FF
H.R.‡	0.089	0.080	11	0.080	0.080	0		Three fingers	Marked
M.R.	0.101	0.072	40	0.078	0.093	0	2.0+†		I – FF
G.S.	0.089	0.071	25	0.055	0.073	−1	2.8+†		I – FF
H.L.	0.047	0.035	34	0.061	0.065	2	2.5+†		1 – FF
M.R.	0.069	0.059	17	0.078	0.083	−2	1.3		0

*MVA: Mitral valve area.
†I and insufficiency plus forward flow.
‡Postoperative traumatic surgical condition at end of operation.
I: Insufficiency. FF: Forward flow.

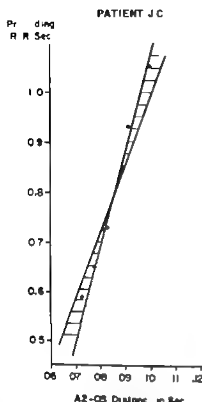


Fig 1 Discrepancy in the choice of slopes. I Patient J C the scatter of the A_2-OS intervals would permit some latitude in establishing slope. The range of slopes is illustrated This range actually represents variation in A_2-OS shortening of only 10 per cent.

The second patient (W B) had marked shortening of her A_2-OS interval with exercise (100 per cent) Because of a long A_2-OS interval (0 088 second at a rate of 75) she had a Wells index of −1 Clinically she had been asymptomatic until she experienced a bout of pulmonary edema after exertion The third patient (M.S.) had a Wells index of 0 but a significant reduction (58 per cent) in the A_2-OS interval

Two of 3 patients with moderate stenosis but with significant regurgitation had Wells indices of 2 and 3 whereas in all 3 the per cent shortening of the A_2-OS interval was less than 35

In the 8 patients with a dominant mitral insufficiency the change in the A_2-OS interval varied from 11 to 40 per cent It was highest in the patient with the smallest valve area (Patient M R —2.0 sq cm) In 7 patients the Wells index varied from −3 to 0 accurately reflecting the insignificant gradient across the mitral valve In the eighth patient (H L.) it was +2 (Fig 3) This patient did have a significant mitral gradient (20 mm Hg) despite an estimated mitral valve area of 2 6 sq cm

In one patient (M R) with significant mitral stenosis (0 9 to 1.3 sq cm.) the A_2-OS interval was little altered However this patient had concomitant aortic stenosis with an aortic valve area of 0 85 sq cm and a systolic gradient of 38 mm. Hg Her left ventricular end-diastolic pressure was 16 mm Hg The aortic lesion was undoubtedly the dominant one. The Wells index also reflected the lack of significance of the mitral lesion

It could be predicted from our data that the plot of A_2-OS against R R would over a wider rate range be a reversed sigmoid curve Slopes for the estimation of the per cent shortening of A_2-OS were established from its straight central portion Craige and Murray* were aware of the inaccuracy of conclusions based on long cycles, although their upper limit of 1 second for the R R interval may be too stringent and has not been used

*y = Hyperbolic sine x.

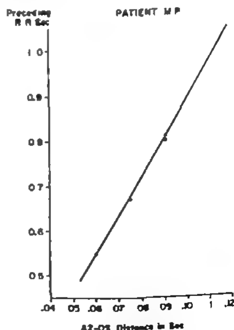


Fig 2 Marked degrees of change in A_2-OS intervals. Patient M P had the severest lesion of the series. His A_2-OS distance is quite long (0 089 sec) at heart rate of 75 It shortens abruptly with increase in rate

A 50 per cent shortening of the A_2-OS interval was taken as suggestive of a dominant obstructive lesion of the mitral valve.

Discussion

The assimilation of knowledge from catheterization and surgery has led to an appreciation of the presence of the opening snap in both mixed mitral lesions and pure insufficiency.[8] This evolution of ideas has been well summarized by Nixon Wooler and Radigan[1] who attribute the formation of the opening snap to the mobile aortic leaflet of the mitral valve. Unfortunately the presence of such an opening snap allows no conclusions as to the type of marginal fixation of the leaflet.

Wells, extending the thoughts of previous authors,[11,12] has attempted to utilize the Q-M interval to separate out from the A_2-OS interval the factors other than the mitral gradient. He further tried by correcting to a standard rate to eliminate this as a factor. The theory was excellent, particularly in that the loud M of mitral stenosis may be a mitral everting snap as suggested by Sellors[18] and Belcher. Practical evaluation of the index of Wells (Q-M minus A_2-OS expressed as a unit for each 1/100 of a second difference) in this study as well as in many others, has revealed agreement with the general relationship yet resulted in the rejection of the diagnostic value in the individual cases. Wells used a fixed rate in the determination of his index. Hence, he discarded the alteration in timing with the change in gradient which occurs when the output and the diastolic filling interval are altered. Many observers have attempted to utilize the variation in the A_2-OS and/or Q-M interval with exercise in order to evaluate the severity of mitral stenosis. Bayer and associates[4] unfortunately ignored the rate factor entirely and because of this their method has found limited acceptance here and in England despite its potential value. Pinardi and Ström studied the A_2-OS variation with exercise and correlated it with catheterization data from the right side of the heart. Their Figure 3 shows a fairly consistent slope for the majority of their patients. They did not comment on this fact. They

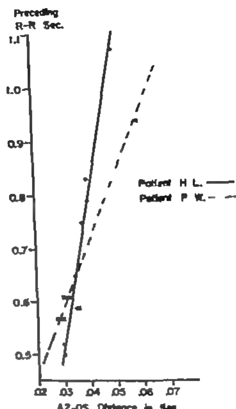


Fig. 3. Rates of change in initially short A_2-OS intervals. The extremely short A_2-OS intervals in Patients H L. and P W. are illustrated. In H.L. the distance is relatively fixed. One might postulate limited arc of motion of the aortic cusp as partial explanation, along with high end-systolic gradient, for the short interval. In Patient P W. the A_2-OS interval, although short already is appreciably decreased by exercise.

did note that at times the scatter (of results) was however increased by relating the time intervals to a common heart rate.[17]

Both Kelly[8] and Julian and Davies consider the electromechanical interval of the left ventricle to be a potential source of error in the determination of Q-M intervals, even in normally conducted beats. A significant drawback to the use of the Q-M interval in practice is the identification of the exact onset of the mitral first sound. Some authors have Q-M intervals outside of the accepted range.[22] A loud delayed tricuspid first sound after low frequency presystolic and early systolic sounds can be confused with the mitral closing (everting) sound. Ejection sounds an electrocardiographic lead recorded paral

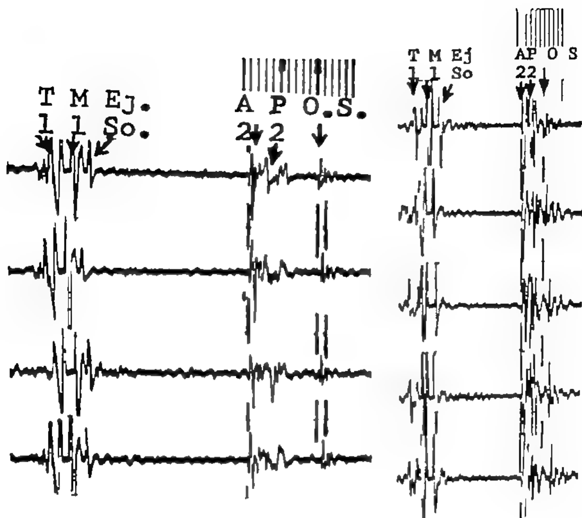


Fig 4 Illustrative tracings of interval measurements. Pre-exercise (*left*) and postexercise (*right*) records in Patient W B Fine time lines are 0.01 sec. apart heavier lines are 0 05 sec. apart. Both records illustrate the sharp onset of the second sound and the opening snap. The pre-exercise record shows four consecutive cycles cut from a single sound channel. The rate is constant. The A_2-OS interval varies from 0 093 to 0.098 sec. The postexercise record from the same channel shows the gradual increase in the A_2-OS interval from 0.048 to 0 068 sec., with slowing of the rate from the immediate postexercise high (Tracings were retouched for reproduction.)

lel to the null plane of the initial axis of the QRS and the diminution in size of M_1 with calcification of the valve reduce further the accuracy While considerable skill in obtaining recordings, as well as the use of multiple channels of sound and pressure improve the measurement, the A_2-OS interval may be determined with greater accuracy

We have equated a postexercise change in rate with shortening of the diastolic filling time and an even more significant increase in output [3] A given increase in rate and output is better tolerated in insufficiency than in stenosis, and the rise in atrial pressure is more marked in the latter condition This yields in mitral stenosis a greater early diastolic gradient and shorter A_2-OS interval Kuo and Schnable (quoted by Moret and associates[22]) observed a lack of variation in the A_2-OS interval when severe mitral insufficiency and/or aortic insufficiency accompanied mitral stenosis. Moret and his co-workers verify this in general Incomplete emptying of a failing left ventricle probably limits variations in the A_2-OS interval The present study shows

that a mixed mitral lesion in which stenosis dominates will produce a variable A_2-OS interval

It would seem from the available data that shortening of the A_2-OS interval as previously defined constitutes a fair estimate of the significance of the mitral obstruction in the picture of over-all cardiac function. It must not be assumed that this can approach the accuracy of quantitation of forward and regurgitant flow and the response to exercise It would be affected too by the state of the myocardium at the time of examination (Patient J.M) It is unreasonable to expect that individual variation will not cause some overlap in grouping (Patients M R. and M W) Further experience may reveal paradoxical responses.

Summary

The mitral opening snap commonly occurs in mixed mitral lesions and not infrequently in pure mitral insufficiency The reduction in the A_2-OS interval with lowered diastolic filling time and increased output is related to the mitral valve gradient and indirectly to the size of the mitral orifice. A marked reduction in the A_2-OS interval with increasing rate and exercise appears to suggest dominant mitral stenosis. This observation is of value in relating clinical and catheterization observations.

A comparison is made with the index of Wells.

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Fig. 1. Transmural configuration of myocardial ischemia. Systemic left ventricular and coronary pressures normal. Control experiment: separate perfusion of left main coronary artery (Method A). Unintentional occlusion of septal artery during placement of coronary perfusion cannula. *Solid black:* Stained (i.e., perfused) regions of heart muscle. *Stippled:* Unstained (i.e., totally ischemic) regions of heart muscle. Section at base of left ventricle at right angles to septum. Right ventricle not d

pe ... about 50 ml. of 2 per cent sodium fluorescein in saline was injected intravenously. About 5 minutes after the dye had been injected, the experiment was terminated by an intravenous injection of KCl, the chest was then opened, and the heart was excised and examined. The heart muscle was stained uniformly.

In 4 other experiments the left main coronary artery was cannulated as described in Method A and the coronary perfusion pressure was set at 60 mm. Hg. With the coronary pressure fixed at this low level, the inflow into the right side of the heart was diminished at the same time so that the LVDP remained below 8 mm. Hg. The left ventricular myocardium was stained uniformly.

In 5 experiments severe failure of the left ventricle was intentionally reproduced as described in Method A. The highest LVDP maintained during a steady state was 40 mm. Hg. In this group of experiments the coronary perfusion pressure was fixed at levels above 90 mm. Hg. The left ventricular myocardium was stained uniformly.

In 3 experiments severe left heart failure was intentionally reproduced with the LVDP at or above 25 mm. Hg and the coronary perfusion pressure at about 55 mm. Hg. It was known (see below) that such a pressure pattern would cause ischemia of massive, confluent inner layers when the pericardium was closed. However, in the 3 experiments described here the pericardium was widely opened after the LVDP had risen above 25 mm. Hg. As soon as the pericardium was incised, the heart's volume increased and the LVDP fell toward normal. The myocardium was then marked as described in Method A. In 1 experiment small patches of unstained heart muscle were distributed throughout the left ventricular wall except only the immediate subepicardial region. In the other 2 experiments the heart muscle was stained uniformly.

When a major coronary vessel had been totally occluded before addition of the marker dye to the blood, the unstained region of heart muscle assumed a transmural configuration. Unintentional occlusion of the septal artery caused by a technical error during the cannulation of the left main coronary artery left a similar transmural region unstained in the septum (Fig. 1). When the cross section of a major coronary vessel had been constricted excessively (3 experiments with



Fig. 2. Patchy subendocardial ischemia of left ventricular wall. Method A. LVP = 92/16 mm. Hg. Coronary perfusion pressure (CP) = 70 mm. Hg. Heart inflow (CO) during experimental period = 63 ml./kg./min.



Fig. 3. Total, concentric, confluent ischemia of inner layers of left ventricular wall. LVP = 78/23 mm. Hg. CP = 55 mm. Hg. CO = 47 ml./Kg./min.

coronary stenosis, Method B), the unstained heart muscle mass involved the entire thickness of ventricular wall and was similar in appearance to that seen after coronary occlusion.

2. Ischemia of inner layers during separate perfusion of the left main coronary artery. When the coronary perfusion pressure was between 60 and 75 mm. Hg and when the LVDP was steadily above 20 mm. Hg during the experimental periods (4 experiments), discrete patchy unstained areas were present in the papillary muscles and the left ventricular wall adjacent to the endocardium (Fig. 2). In experiments with a coronary perfusion pressure between 45 and 55 mm. Hg and LVDP between 25 and 35 mm. Hg (5 experiments), the unstained regions of heart muscle became confluent (Fig. 3). The most severe state of ischemia of stratified inner layers seen here involved the inner two thirds of the left ventricular wall including the septum (Fig. 4). The confluent stratified unstained regions of heart muscle were adjacent to the endocardium and did not reach the epicardial surface or the right ventricular endocardial surface of the septum. The proportion of unstained heart muscle appeared to increase with decreasing coronary perfusion pressure and increasing LVDP. Coronary perfusion pressures below 45 mm. Hg were not examined because steady cardiac performance at such low coronary pressures was not observed when the LVDP was above 15 mm. Hg.

3. Ischemia of inner layers caused by stenosis of coronary arteries. Unstained regions of heart muscle were observed in experiments with Method B only when the cross-sectional area of a major coronary vessel had been constricted to a diameter corresponding to that of a gauge 22 needle or smaller (6 experiments). Left heart failure (LVDP above 12 to 15 mm. Hg) could be produced readily when the blood volume was expanded after the coronary vessel had been constricted. When the heart was arrested 5 to 15 minutes after addition of the marker dye to the systemic blood, it was found that stratified regions of the heart muscle had remained unstained. The unstained regions were adjacent to the ventricular cavity and were located in the territory supplied by the constricted vessel. The outer layers of ventricular wall were stained uniformly in these experiments (Fig. 5). However, when a major coronary vessel had been constricted and when the blood volume was *not* expanded, the LVDP did not rise above 10 mm. Hg, only patchy, discrete unstained regions of heart muscle were then observed in the subendocardial region.

Discussion

Criticism of the method. During the excision of the heart at the end of an experiment, precautions were taken to prevent

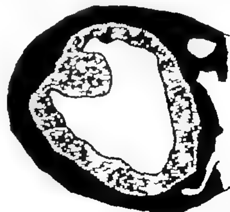


Fig. 4. Total, concentric, confluent ischemia of inner layers of left ventricular wall. LVP = 67/32 mm. Hg. CP = 45 mm. Hg. CO = 32 ml./Kg./min.



Fig. 5. Regional ischemia of inner layers caused by stenosis of left anterior descending coronary artery. Estimated cross-sectional area of lumen at site of constriction = outer diameter of gauge 23 hypodermic needle. Site of constriction 1.3 cm. distal from bifurcation of left main coronary artery. Systemic arterial pressure = 125/110 mm. Hg. LVP = 102/12 mm. Hg. Four representative transverse sections through left ventricle taken at a distance of about [illegible] cm. apart from each other. Note increasing size of totally ischemic region near apex.

inflow of labeled coronary blood into regions of heart muscle that had been deprived of coronary blood supply while the heart was beating in situ. In order to avoid such artifacts, the separate coronary blood conduit was occluded and the base of the heart was cross-clamped before the heart was excised.

There can be no doubt that unstained regions of heart muscle shown here were not reached by dye-labeled blood under the conditions of the experiments. It is conceivable that the absence of marked blood in the inner layers could have been referable to technical artifacts: a heart might have been excised as soon as the dye-labeled blood had stained the epicardial surface but before it had reached the inner layers of ventricular wall. This potential source of error was not a factor in our experiments: it was avoided by permitting 2 to 10 minutes to elapse between injection of the dye and the last heartbeat. The unstained regions of heart muscle will therefore be designated as "totally ischemic" for purposes of further discussion.

An open pericardium caused abnormally low LVDP and abnormally large cardiac volumes. For this reason all conclusions drawn here stem from experiments in which the pericardium was virtually closed.

Factors causing total ischemia of inner layers of ventricular wall. Thick confluent layers of totally ischemic heart muscle were seen only when two hemodynamic abnormalities existed at the same time: low coronary perfusion pressure and abnormally elevated LVDP. When coronary pressure was controlled by the separate perfusion technique (Method A), the confluent layers of ischemic myocardium had a concentric appearance and involved the papillary muscles as well as the inner shells of ventricular wall. When local coronary pressure was reduced by an experimental coronary stenosis (Method B), the ischemic layer of subendocardial heart muscle was confined regionally. The subendocardial localization of ischemic muscle is explained by the relationship of the local coronary and intramyocardial diastolic pressures. Earlier measurements of Johnson and DiPalma demonstrated increasing gradients of intramyocardial pressure from the epicardial to the endocardial regions of heart muscle. The method of Johnson and DiPalma had been criticized, but their conclusions have now been confirmed by the more accurate techniques of Laszt and Müller.[4] It has also become apparent from analyses of the determinants of coronary flow[4] that the inner layers of heart muscle are reached by arterial blood only in diastole because this is the only period of the cardiac cycle during which local coronary pressure exceeds local intramyocardial pressure. Our data afford evidence for this thesis: any region of heart muscle will be totally deprived of coronary blood supply whenever local intramyocardial pressure remains higher than local coronary pressure even during diastole. From experiments published elsewhere we knew that in dogs the Thebesian vessels make no significant contribution to the blood supply of the left ventricular wall.

"Thebesian" blood flow into the left ventricle was not evident here.

The inner layers of left ventricular wall became totally ischemic when low coronary artery pressure and high LVDP existed at the same time. The components of this pressure pattern were reproduced in several different ways. Coronary pressure was altered by separate perfusion of the entire left coronary territory at a known low pressure stenosis of a major coronary vessel when the pressure distal from the constriction was not known but must have been lower than the central coronary pressure systemic hypotension induced and controlled by an arterial reservoir (data not reported here) High LVDP was caused when the pericardium was closed and when reduced coronary pressure coexisted with fixed or with increased inflow into the heart or with expanded circulating blood volume Other potential precipitating factors, such as tachycardia (with the attending residual contraction between beats and high LVDP) anemia, or hypoxia were not examined here but are not excluded by the data.

Not only confluent layers but also discrete patches of subendocardial ischemia could be explained by an excess of local intramyocardial pressure over local coronary pressure the abnormal pressure differentials were of lesser magnitude However another mechanism could not be excluded as a cause of such "patchy" subendocardial ischemia it is possible that patchy ischemia of the inner layers, particularly when caused by coronary stenosis or low coronary perfusion pressure in the absence of elevated LVDP can be caused by widely patent coronary sphincters[11] which permit the outer layers of the heart to pre-empt most of the available coronary blood supply at the expense of the inner layers.

Significance of the data reported here That injury confined to the inner layers of heart muscle can occur as a consequence of ischemic heart disease had been clearly expressed by earlier authors. Confusion had arisen because hemodynamic features of the condition had not been comprehensively described most reports were concerned mainly with morbid anatomic electrocardiographic and clinical findings. The evidence reported here identified some but probably not all hemodynamic conditions which deprive the inner layers of left ventricular wall of their supply of blood Earlier authors were interested in subendocardial ischemia primarily because it was believed to cause pain and electrocardiographic changes characteristic of angina pectoris the data reported here are not considered to be pertinent to this problem

The experiments afford significant conclusions concerning the influence of ischemia of the inner layers on cardiac dynamics. When ischemic the inner shells of heart muscle cannot contribute to the contractile performance of the heart. This situation is critical not only because it reduces the contractile strength of the heart as a whole but also because the function of vital intracardiac structures is impaired as demonstrated by continuous recording of chorda tendinea tension[12] When ischemic the papillary muscles cannot contract functional mitral regurgitation will result The bundle of His and other parts of the intraventricular conduction system cannot function without adequate nourishment even the excitation of exterior adequately perfused layers of heart muscle will be impaired The experiments described here also invite the inference that the decreasing contractile strength commonly observed in intact ventricles during increasing LVDP (descending limb of the pressure-volume diagram of a beating ventricle) may be caused by ischemia of the inner layer of the ventricular wall.

Clinical conditions which can set the stage for the onset of ischemia of the inner layers would appear to be (1) circulatory overloads in patients with coronary stenosis, and (2) cardiogenic shock, especially when the filling pressure of the ventricles is elevated In these clinical situations we would expect episodes of ischemia of the inner layers to initiate vicious cycles that result in rapid deterioration and death Even when they have not led to sudden cardiac arrest or ventricular fibrillation hemodynamic conditions which cause ischemia of the inner layers will have left irreversible myocardial damage after per

sisting for 30 to 60 minutes. This type of massive cardiac insult cannot be expected to leave traces because death will occur so rapidly that morphologic changes cannot take place; this may explain why acute massive ischemia of the inner layers has escaped detection for so long. Less extensive necroses have been noticed because the injured hearts were able to survive.

Patients with acute coronary disease are often treated with pressor agents; certain experimental treatments have been proposed with the expectation that coronary flow must vary with the coronary arterial pressure. However, the coronary pressure distal from stenotic segments may increase very little even after large increments in systemic arterial pressure. If and when an increase in systemic arterial pressure is "purchased" at the cost of further elevations in the LVDP, the prognosis for some patients with coronary stenosis will be influenced unfavorably because their ischemic myocardium will receive less blood than before. Our data suggest that, in patients with acute heart failure, interventions that diminish LVDP while maintaining a barely adequate blood pressure may be more effective than therapeutic maneuvers that raise both blood pressure and LVDP.

Summary

Regional blood flow in heart muscle was studied by adding a dye to coronary blood. The pericardium was closed. Coronary and aortic pressures varied independently and were controlled. When the left ventricular diastolic pressure (LVDP) was intentionally elevated above 25 mm. Hg and when the coronary arterial pressure was reduced below 0 mm. Hg at the same time, extensive sheets of heart muscle remained unstained by the marker dye, indicating that the inner layers of the left ventricular wall had been deprived of their supply of blood while the heart was beating. Ischemia of the inner layers must be explained by an excess of local intramyocardial pressure over local coronary pressure, that persists even in diastole. Ischemia of the inner layers may explain the "descending limb" of the systolic pressure-volume diagram which is regularly observed in beating ventricles but not in heart muscle strips. Ischemia of the inner layers of ventricular wall can initiate vicious cycles that cause sudden death in persons with coronary stenosis. Ischemia of the inner layers is a cause of irreversible cardiac damage that can terminate life suddenly without leaving obvious traces that can be detected at autopsy.

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The effect of exercise on pulmonary blood volume

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The relationship between cardiac output and the volume of blood in the lungs has received considerable attention in the past several years. Both central blood volume and cardiac output can be measured using the dye-dilution method. Injection into a peripheral vein and sampling from an arterial site is a technique commonly used for determining cardiac output. However, the objection to this technique in the recording of central blood volume is that it measures a large volume, only part of which is in the lungs. The limits of this large volume are difficult to determine anatomically, and appear to increase with exercise. Efforts to improve the technique involve injection closer to the pulmonary artery and sampling closer to the pulmonary veins. Another approach has been the use of a double injection into the pulmonary artery and left atrium with sampling from an arterial site. Methods such as these, although useful in narrowing the volume measured, have not been applied to large numbers of normal subjects because of the inherent risks.

External monitoring of a radioactive substance offers a safe method of measuring the volume contained in the heart and lungs. Previous studies in this laboratory have demonstrated the reproducibility of this technique which can be applied to normal subjects. The present investigation was designed to apply this method in order to determine the effect of exercise on the central circulating blood volume measured in normal subjects with and without ganglionic blockade and in patients with compensated heart failure.

Methods

Hospitalized male patients from the general medical service of the Syracuse Veterans Administration Hospital served as the control subjects. All were without evidence of cardiovascular disease as determined by clinical history and physical examination. All patients who were over 40 years of age had a normal chest x-ray film and electrocardiogram.

Seventeen patients with heart disease were also studied. All but one had been in frank congestive failure; the exception was a man without cardiomegaly by x-ray examination but with an aortic valve gradient of 50 mm. Hg and a calculated valve area of 1.6 sq. cm. At the time of the study all were ambulatory and able to lie flat. Only 2 were not on digitalis. All subjects were studied in the fasting state and without sedation.

The details of the method have been

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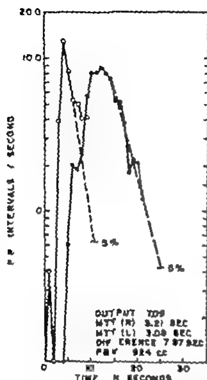


Fig. 1. Dilution curves recorded by external counting. Open circles are values obtained from the probe on the right side. Solid circles are those obtained from the probe on the left side.

scribed in a previous publication. During the present study, two-inch thallium activated sodium iodide crystals were used.* Two external probes were centered over the right heart border and left apex and connected to spectrometers. The primary gamma radiation of I^{131} was recorded (0.364 Mev midpoint with a window of 0.050 Mev) in order to minimize the counting of backscatter. The indicator was I^{131} Diodrast in a dosage of 30 and 50 microcuries. If a third determination was performed, 70 microcuries were used. Injection was performed via a polyethylene catheter† whose tip was in an axillary vein, followed by a rinse of 20 ml. of dextrose in water. Cardiac output was measured by indicator-dilution technique using interrupted arterial sampling. The impulses from the spectrometers were transmitted to scalers and recorded on an oscillograph along with the time of injection and the cardiogram. The frequency was plotted on semilogarithmic paper and the mean transit time was calculated for indicator passing through each side of the heart. The mean transit time of the probe on the right side was subtracted from that of the probe on the left, and the difference was multiplied by the cardiac output to give the intrathoracic blood volume (Fig. 1). This volume includes part of the cardiac volume but is termed *pulmonary blood volume* (PBV).

The mean transit time from the catheter to the arterial sampling site included that of a 10-cm. length of tubing attached to the Cournand needle. This time multiplied by the cardiac output gives the central blood volume (CBV).

The patients were supine with both feet on pedals which later served as the exerciser. The feet were slightly higher than the trunk in the resting state. Alternate flexion and extension of the legs raised and lowered weights. The force exerted on each pedal was 5 kilograms and the distance moved was 25 cm. All patients performed exercise for 3 minutes at a frequency of 90 per minute. Injection for the measurement of PBV and cardiac output was performed within 5 seconds after the cessation of exercise.

A trial of exercise was performed by all patients prior to insertion of the needles and placement of the probes. The patient then rested for at least 20 minutes, during which time the needles were inserted and the apparatus was arranged. Repeat determinations were made at least 10 minutes apart.

Partial ganglionic blockade was produced in 7 control subjects with an infusion of trimethaphan camphorsulfonate.‡ Sufficient trimethaphan was used to produce either a fall in mean blood pressure§ of 15 mm. Hg or a rise in pulse of 15 per minute. All experienced a dry mouth and all received at least 3 mg. per minute of trimethaphan (mean 6.6 mg./min.). The subjects were studied at rest, after at least 3 minutes of blockade, and finally with exercise as ganglionic blockade was continued. The blood pressure used was determined by auscultation immediately after injection for the cardiac output.

*Nuclear model 1810, Nuclear Corp., Chicago, Ill.
†PE 190, Clay Adams Co., New York, N. Y.

‡Hoffmann-La Roche Company, Nutley, N. J.
§Diastolic pressure plus one third of the pulse pressure.

Table I *Response to exercise in control subjects*

	Heart rate		*Cardiac index*		*PBV/M*		*SV/M*		*CBV/M*	
	R	*Ex*	*R*	*Ex*	*R*	*Ex*	*R*	*Ex*	*R*	*Ex*
Mean	78	99	4 25	6 12	539	507	[illegible]	63	1 42	1 73
Change	+21		+1 87		−32		+7		+0 [illegible]	
S D	22		1 29		20		3 8		0 28	
P	<0 05		<0 01		<0 01		<0 005		<0 05	

R: Resting value, Ex: Exercise value PBV/M Pulmonary blood volume (ml/M² BSA) SV/M. Stroke volume (ml M² BSA) CBV/M Central blood volume (liters/M² BSA)

Table II *Normal subjects with exercise and ganglionic blockade*

	Heart rate			*Cardiac index*			*PBV/M*			*SV/M*		
	R	*B*	*Ex*	*R*	*B*	*Ex*	*R*	*B*	*Ex*	*R*	*B*	*Ex*
Mean	76	80	92	3 94	3 76	4 74	491	457	540	53	48	54
Change		+4	+12		−0 18	+0 98		−34	+83		−5	+6
S.D		15	10		0 62	0 68		92	83		10	7
P		NS	<0 05		NS	<0 01		NS	<0 05		NS	NS

R Resting value B Ganglionic blockade Ex Exercise value NS: Not significant

Tracings were obtained for reproducibility in the patients with heart disease in 14 cases, and in patients with heart disease and exercise in 15 cases.

Results

Of 14 control subjects 7 were studied at rest and with exercise. Seven were studied at rest, with partial ganglionic blockade and finally with exercise as blockade continued. The mean PBV for the 14 subjects studied at rest was 515 ml /M (S.D ± 98)

The individual data of the rest and exercise measurements are presented in Table I and Fig 2. With the exercise, the 7 control subjects all had an increase in cardiac index the mean rise was 1 98 L. min /M (S D ± 1.29) a mean rise of 44 per cent Stroke volume rose in all (mean rise of 7 ml./M²) and pulse rose in all (mean rise of 21 per minute) PBV fell in all the mean fall was 32 ml./M (S.D ± 20) Central blood volume as determined by the Stewart Hamilton method rose in 6 the mean rise was 310 ml /M

Table III *Reproducibility of PBV in patients with heart disease*

	Cardiac index		*PBV/M*	
	I	*II*	*I*	*II*
Mean	3 47	3 55	609	623
Change	+0 08		+14	
S D	0 42		143	
P	NS		NS	

The data of the blockade are presented in Table II and Fig 3 With the trimethaphan alone mean blood pressure fell in 6 subjects (mean fall of 24 mm. Hg) The one subject whose blood pressure rose slightly had a rise in pulse of 16 per minute. The effects found on output pulse, PBV and stroke volume were variable With blockade continued and with exercise the mean blood pressure fell further in 5 sub-

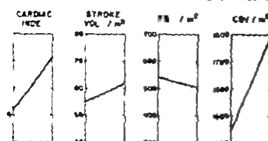


Fig 2 The left-hand side of each block shows the resting value and the right-hand side shows the value with exercise.

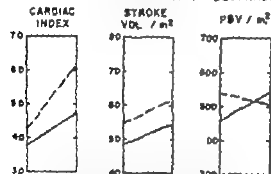


Fig 3 The dashed lines represent the data illustrated in Fig 2 (control subjects). The left hand side of each block shows the resting value and the right hand side shows the value with exercise.

jects Cardiac index rose in 6 of 7 the mean rise was +0 98 L. min./M² (S D ± 0 68) (+26 per cent) PBV rose in 6 the mean rise was +83 ml /M² (S D ± 83)

Data for reproducibility of pulmonary blood bolume in patients with heart disease are presented in Table III and Fig 4 The mean values for the first and second determinations were 609 and 623 ml./M² respectively but with a standard deviation of the change of ± 145 ml./M² Exercise in the patients with heart disease (Table IV and Figs. 5 and 6) produced a rise in cardiac index of 1 40 L./min./M² (S D ± 0 88) (+41 per cent) Pulse rose a mean of 19 per minute Stroke volume rose a mean of 7 ml./M² Pulmonary blood volume rose in 13 of the 15 subjects (mean rise of 106 ml./M²) (S D ± 127)

The changes in stroke volume and PBV with exercise in the various groups are summarized in Fig 7

Discussion

The response of PBV to exercise has been of considerable interest in the past several years. The Stewart Hamilton central blood volume has been shown to rise with exercise in most normal subjects. Mitchell and associates[3] found an increase in all of their determinations. The exercise used was more strenuous producing a rise in cardiac output of 289 per cent Braunwald and Kelly[4] showed a rise in 8 of 10 subjects as output rose 134 per cent. Ball and associates described a rise in central blood volume in 7 of 9 subjects whose output rose 31 per cent. Mankin and Swan[5] produced a rise in output of 53 per cent CBV rose in 11 of the 12 with a mean rise of 19.3 per cent. Thompson and associates[6] noted a doubling of cardiac output with exercise and a mean rise in central blood volume of 42 per cent. Although the exercise as used in the present study was mild producing a rise in cardiac output of 44 per cent the degree of exercise is comparable to the level used by Ball Mankin and Thompson

Table IV Exercise in patients with heart disease

	Heart rate		Cardiac index		PBV/M		SV/M	
	R	Ex	R	Ex	R	Ex	R	Ex
Mean	74	93	3 41	4 81	585	691	46	53
Change	+19		+1 40		+106		+7	
S D	9 5		0 88		127		7 5	
p	<0 001		<0 001		<0 02		<0 02	

R Resting value. Ex Exercise value.

In the present study CBV rose in all. The PBV as recorded by the present technique demonstrated a consistent fall with exercise in normal subjects the mean fall was −6 per cent. Similar results have been reported by Lammerant[7] (−17 per cent) with supine exercise, and by Moir and Gott[4] (+1 per cent) both using external monitoring but with somewhat different techniques.

The technique of external monitoring does not fulfill the ideal of recording the volume contained only in the lungs, for it certainly includes at least part of the cardiac volume. Using the technique of injection into the pulmonary artery and into the left atrium McGuire and associates and Milnor and associates recorded pulmonary blood volumes lower than those in the present study.

Thus, the decrease in heart size which has been reported to occur with exercise[1] may contribute in part to the decrease in PBV as noted in this study.

The reasons for the difference in response of CBV and PBV appear to lie in the compartments included in the CBV. Marshall and Shepherd[12] have demonstrated a rise in CBV with exercise. However it was possible to decrease this volume by warming the extremity from which the sampling was done. Gleason and associates[13] reported similar findings by sampling from two sites. When the flow to one was increased the CBV as measured in that extremity was decreased.

Marshall and Shepherd[12] have been able to narrow the limits of the CBV in the dog. Using injection into the pulmonary artery with sampling close to the aortic valve and using high rates of flow they showed that CBV rose only 7 per cent when output was almost tripled. Thus the arterial component of the CBV does vary and can be a source of error with increasing levels of output, particularly if only part of the organism is exercised.

Franklin and associates, using the method of recording the output of both the right and left ventricles in the dog found that the output of each increases immediately with exercise without a time lag in the left ventricle. This would suggest that the left ventricular output is not dependent on an increase in pulmonary blood volume,

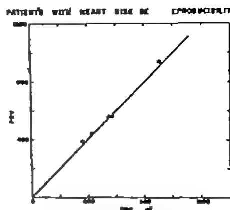


Fig. 4 Both studies were performed at rest, the first PBV on the abscissa and the second PBV on the ordinate. The line is that of zero identity.

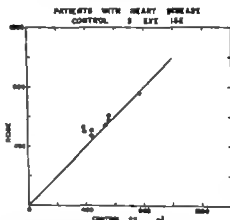


Fig. 5 The first PBV study (abscissa) was done at rest. The second study (ordinate) was performed immediately after exercise. The line is that of zero identity.

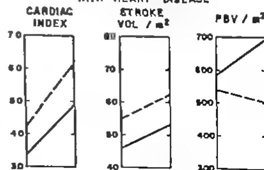


Fig. 6 The dashed lines represent the data illustrated in Fig. 2 (control subjects). The left-hand side of each block shows the resting value, and the right-hand side shows the value with exercise.

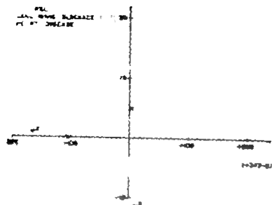


Fig. Effect of exercise on changes in stroke volume and pulmonary blood volume. Changes in PBV are plotted on the abscissa and the changes in stroke volume on the ordinate.

and that the amount of blood in the lungs was not increased, at least for the first few beats at the onset of exercise.

The rise in PBV with exercise in 13 of the 15 patients with heart disease in this series is similar to the results obtained by the Stewart-Hamilton method. Ball and associates, using CBV, found an increase of 300 ml./M. in patients whose resting cardiac index was greater than 2.5 L./min./M. Rappaport and associates[16] found that, with exercise, CBV rose in 4 patients with mitral stenosis but did not rise in 3 in whom the cardiac output did not change significantly. Moir and Gott found that PBV in patients with mitral stenosis fell with exercise and rose in only 1 of 8.

The group of patients with heart disease was not homogeneous and demonstrated large variations in PBV. The mean PBV at rest was larger in the patients with heart disease than that in the normal subjects. The mean for the 14 normal subjects was 515 ml./M. (S.D. ± 98). The patients with heart disease had a mean of 585 ml./M. (S.D. ± 1 6). This difference is not significant ($p > 0.20$). This is similar to findings reported by Kopelman and Lee, by Ball and associates[4] using the usual Stewart-Hamilton method, and by those using the precordial monitoring method. Moir and Gott report the mean for normal subjects as 610 ml./M.² (S.D. ± 168) and that for patients with mitral stenosis as 678 ml./M. (S.D. ± 190). Love and associates[17,18] report the normal mean as 490 ml./M.² (S.D. ± 130) and that in heart disease as 520 ml./M.² (S.D. ± 150). Thus the mean for the patients with heart disease tends to be higher, but for no single series are the differences significant. The only exception to this is the study by Borden and associates[19] which showed no significant difference in CBV between patients with valvular heart disease and normal subjects, but a significant increase in those with other forms of heart disease.

Previous efforts in this laboratory[2]* to change the PBV with an antigravity suit and with drugs have shown it to vary within narrow limits. Therefore, we decided to investigate the role of the autonomic nervous system.

In normal subjects with partial ganglionic blockade a significant effect was obtained as measured by the fall in total peripheral resistance (mean change of −226 dynes sec. cm.⁻⁵). Indeed, the end point of dosage in drug-induced blockade is necessarily arbitrary. In this study we desired to produce a minimal but significant effect.

During partial blockade the increase in PBV with exercise suggests that the pulmonary vascular volume is regulated at least in part by neurogenic influences. The data of Franklin and associates suggest some rapid controlling system of left ventricular output which is independent of right ventricular output and very likely due to neurogenic activity.

Fig. 7 shows the change in stroke volume versus the change in PBV. Exercise in the normal subjects uniformly produced an increase in stroke volume but a fall in PBV. Twelve of the patients with heart disease showed an increase in stroke volume and an increase in PBV.

It is postulated that in the patients with heart disease cardiac output and stroke volume can increase with exercise but only at the expense of an increase in PBV. Although pressures were not measured, it is suggested that the patients with heart disease could increase cardiac output only at the expense of increasing diastolic filling pressure and cardiopulmonary volume.

Conclusion

By means of a precordial monitoring technique, intrathoracic blood volume was

measured before and after mild supine exercise.

Control subjects demonstrated a slight decrease in pulmonary blood volume (PBV) with exercise (−32 ml./M.²). The large changes which have been recorded using the Stewart Hamilton method appear to be the result of variations in the circulatory dynamics of other systems as well as PBV.

Subjects with heart disease showed a rise in PBV with the same exercise. Control subjects under partial ganglionic blockade showed an increase in PBV with exercise. It is suggested that the PBV is at least in part under autonomic control and that it is regulated within narrow limits in normal subjects.

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Case reports

Persistent venous valves, maldevelopment of the right heart, and coronary artery ventricular communications

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Persistent venous valves in the right atrium which are large enough to obstruct the tricuspid orifice are extremely rare. Multiple communications between the right ventricle and coronary arteries are also uncommon. This report concerns a case in which both of these anomalies were found.

Case report

A male infant was delivered spontaneously after an uncomplicated pregnancy of 8 months' duration. The mother was a 23-year-old Negro with 2 normal children. At birth the infant weighed 3,480 grams and measured 47 cm. He appeared to be normal until 12 hours of age, when he developed cyanosis and respiratory distress with substernal and intercostal retractions. Chest x-ray examination showed no cardiac enlargement, and the lung fields were clear. The infant choked on his first feeding and subsequently regurgitated water although a gastric tube was passed without evidence of obstruction. At 29 hours of age he became lethargic and assumed a frog position. Respirations were 60 per minute, and the pulse was 128 per minute. Respiratory distress continued and the infant died at 47½ hours of age.

Summary of autopsy report. The infant had dusky cyanosis of the head, neck, chest, and nail beds. There were no abnormalities of the abdominal organs. Multiple petechiae were seen over the epicardial surface, and the pericardial cavity contained a small amount of clear yellow fluid. The heart lay in a transverse position, and the cardiothoracic ratio was 69. The aorta and pulmonary artery arose in their normal relationship to one another but the pulmonary artery had less than one third the diameter of the aorta. An unusually thick-walled, somewhat yellow left anterior descending coronary artery lay in the interventricular groove.

The heart measured 5.2 cm. from base to apex, 4.2 cm. in width, and 2.9 cm. in anterior-posterior diameter. The right atrium was both dilated and hypertrophied; it received the superior and inferior venae cavae and coronary sinus. When the right atrium was opened, the venous valves presented as a continuous broad membrane which overlay the atrioventricular orifice (Fig. 1). The narrowest part of the membrane was 1 mm. in width at its attachment to the septum spurium. There was an elliptical opening 0.4 by 0.2 cm. in the membrane at the orifice of the coronary sinus. Immediately distal to this, the membrane was stretched out to cover the A-V orifice except for an opening 0.4 cm. in diameter which led to the right ventricle (Fig. 1,*A*,*c*).

A relatively large membrane remained to the left of the A-V orifice; this consisted of the left venous valve and a few muscle bundles which arose from the right atrial wall. It was attached at the entrance of the atrial appendage. The foramen ovale was covered by the septum primum, but could be probed to a diameter of 0.6 cm.

From below (Fig. 1,*B*), the membrane was seen to be attached at the superior margin of the A-V ring and was separated from the poorly formed tricuspid valve by a thick ridge of muscle. The septal leaflet, which would have occupied a position immediately inferior to the perforation in the membrane, was absent. Both anterior and marginal

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leaflets were rudimentary and were connected to the ventricles by poorly formed chordae tendineae. A rounded depression in the septal wall was seen at the lower margin of the valve, which corresponded to a slight aortic shelf on the left side of the septum. No ventricular septal defect was present. The chamber of the right ventricle was 0.5 to 0.6 cm. in width and less than 1.0 cm. in depth. The myocardium was hypertrophied and measured 0.7 to 1.0 cm. in thickness. The endocardium was thickened, and the crista supraventricularis was poorly formed. Immediately proximal to the pulmonary valve, the outflow tract of the right ventricle narrowed abruptly to a channel which was less than 0.5 mm. in width and which ended adjacent to the pulmonary valve (Fig. 2,B). There was complete atresia of the pulmonary valve of the diaphragm type, in which three fused cusps were identified. Above the atretic valve the pulmonary artery measured 1.0 cm. in circumference. An elongated, patent ductus arteriosus was present. It had an S-shaped course. Four pulmonary veins entered the left atrium. The ventricular septum was distorted in its superior part to form a slight aortic shelf. The mitral and aortic valves were normal; the left ventricle measured 0.4 cm. in thickness.

CORONARY ARTERIES (Figs. 2 and 3). The left coronary artery arose from behind the left anterior aortic cusp. It gave off a small circumflex branch and continued as the anterior descending artery. A portion of the artery formed a pouch-like structure which gave off a small branch to the myocardium of the left ventricle. At this point, the anterior descending artery was joined by an artery which arose *de novo* from the conus. Immediately distal to their junction the arterial wall became thick, whereas the lumen of the artery was reduced to pin-point size; the artery ended abruptly 1.5 cm. above the apex. At its termination, it lost its thick wall and communicated by circuitous channels with the right ventricle.

The right anterior cusp gave rise to 2 coronary arteries. The largest of these lay in the atrioventricular groove and ended blindly 1.0 cm. from its origin. Immediately distal to its atretic point, the artery commenced anew and gave off two large branches which entered the right ventricle. The second coronary artery arose just anterior to the first, gave off a small branch, and then communicated with the conus by way of a thin endothelial-lined channel. Blood could reach the bulk of the right ventricular myocardium only by way of the right ventricular cavity. The coronary arteries and their communications are illustrated in Fig. 3.

Section through the thickened left anterior descending coronary artery showed extreme intimal hyperplasia of myxomatous connective tissue. The internal elastic membrane was split, and there was an increase in medial elastic tissue. Focal areas of necrosis were seen throughout the trabecular zone of the right ventricle (Fig. 4). These varied from zones of hypereosinophilic muscle fibers with little inflammation to necrosis with neutrophilic infiltration. Such areas were most frequent adjacent to the many sinusoids and arteriovenous connections, but were not limited to these. The myocardium of the left ventricle was normal. The lungs showed aspiration of infected amniotic fluid with early pneumonia; the pulmonary vessels appeared to be normal.

Discussion

Venous valves of the right atrium are normally resorbed sometime between the ninth and fifteenth embryonic weeks (Pat

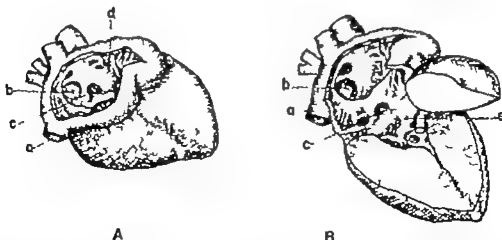


Fig. 1. *A*, Right atrium opened along its anterior surface. Persistent right and left venous valves form an almost continuous membrane in the right atrium. The 4-mm. opening into the right ventricle is seen. *B*, Right atrium viewed from below to show attachment of the membrane. The A-V opening in the membrane is separated from the malformed tricuspid valve by a thick muscle ridge. The right ventricular cavity is small and the wall is hypertrophied. *a*, Inferior vena cava. *b*, Foramen ovale. *c*, Opening into the right ventricle. *d*, Lateral attachment of the membrane to the atrial appendage. *e*, Deformed tricuspid leaflet.

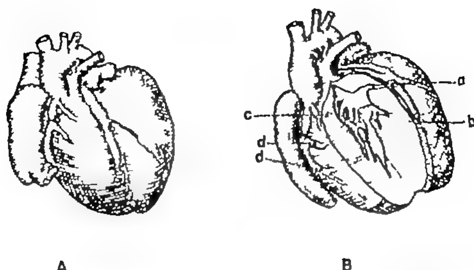


Fig. 2. *A*. Anterior view of the heart, showing the thickened left anterior descending coronary artery with a single small branch. The mai segment of the right coronary artery show point of treula. *B*. Right entricle opened. The conus ends blindly im mediately proximal t the atretic pulmonary al e. *a*. Communication between the left anterior descending coronary artery and ight entricle *b*. Termination of the thickened left terior descending coronary artery and its entrance into the right entricle. *c*. Small accessory branch of right coronary rtery enters right ventricle. *d*. Right main coronary rtery h a point of tresia proximal to its mai branches. Tw of the branches can only be filled w th blood from the right ventricle.

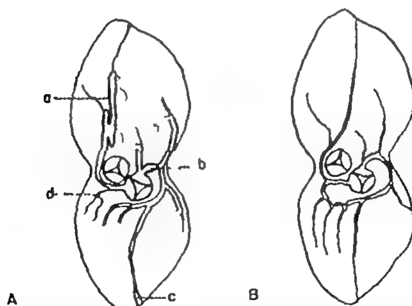


Fig. 3. Diagrammatic sketch of coronary pattern. *A*. Present case Thick ened narrowed segment *a* the left nterior descending coronary artery *b*. Mai right coronary rtery showing tretic segment. *c*. Lumen of the right posterior descending branch obliterated t the pex. *d*. Left circumflex. The dotted lines indicat entrance of the coronary artery int the right tricle *B*. Normal control.



Fig. 4. Area of necrosis in the thickened trabecular zone of the right ventricle (hematoxylin and eosin ×225).

Table I. Coronary artery–right ventricular communications associated with maldevelopment of the right heart

Author Year	*Age Sex*	*Coronary artery communication*	*Tricuspid valve*	*Pulmonary valve*	*Right ventricle*	*Other malformations**
Wilson and Grant, 1925	14 mo. F	RC RV	Malformed flaps	Atresia	Thick	Single ventricle
Craig, 1949	10 mo. F	LC RV	Hypoplastic thickened	Atresia	Thick, 9 mm.	PFO
Williams, et al,[8] 1951	4 days, F	RV RC and left circumflex	Small	Atresia	Thick, 8 mm.	PDA PFO
Kreutzer, et al 1953	1 mo. M	LC RV	Hypoplastic deformed	Atresia	Thick, 8 mm.	PDA PFO
Alexander and Green, 1952	36 hr. F	LC RV	Rudimentary	Conus almost obliterated	Hypertrophied	VSD PDA
Corrarino, et al 1959, Case 3	22 days, F	RC RV	?	Atresia	Hypertrophied	PFO PDA
Gaudiel and Beru, 1960	2 mo. M	LC and RC to RV	Hypoplastic	Atresia	Hypertrophied	VSD PDA
Muir, 1960						
Case 1	3 mo., M	LC RV	Normal	Stenosis	Hypertrophied 10-12 mm.	PDA
Case 2	2 mo. M	RC RV	Hypoplastic	Atresia	Hypertrophied 9 mm.	ASD PDA
Case 3	Stillborn 3 lbs. 12 oz.	RC RV anomalous art. LV communication	Rudimentary rigid ring	Atresia	Hypertrophied, 13 mm.	PDA LVH
Kauffman and Andersen, 1963	47 hr. M	LC RV RC RV	Hypoplastic deformed	Atresia	Hypertrophied, 7-10 mm.	PDA PFO

*PFO, Patent foramen ovale; PDA, Patent ductus arteriosus; VSD, Ventricular septal defect; ASD, Atrial septal defect; LVH, Left ventricular hypertrophy.

ten private communication) Although persisting remnants Chiari's network, are not uncommon broad membranes are rare A review of the literature revealed only 3 cases in which obstructive venous valves are described these were collected by Yater[8] All were in children and were associated with malformations of the right heart

The first case was reported by Leo[19] (1886) the venous valves were sail like with several perforations one of these was 1 0 cm in diameter and opened into the minute chamber of the right ventricle No tricuspid valve was identified and the pulmonary valve was atretic In the second case (Chiari 1897) the right atrium contained a large membrane which was made up of right and left venous valves. The auriculo-ventricular orifice was narrow the tricuspid leaflets were very small and pulmonary atresia was present. The third example was in a 12-day-old girl with cor triloculare biatriatum (Wortmann[22] 1909) Here the membrane consisted chiefly of Eustachian valve but included some of the left valve so that the structure lay over the poorly fashioned and stenotic tricuspid ring Remnants of thickened valvular tissue but no chordae tendineae could be identified The great vessels were transposed It is interesting that the outflow tract of the right ventricle was stenotic in this case even though it led into the aorta rather than the pulmonary artery

The presence of deformed or hypoplastic tricuspid valves in all 4 cases of right atrial valves suggests a causal relationship between these malformations. The concept that currents and pressures of flowing blood affect the development of the heart is widely accepted It seems probable that the flow of blood through the tricuspid ring influences the formation of the valve in the normal embryo and that the baffle effect produced by the persistent atrial valve in altering the normal pattern of flow through the tricuspid ring would lead to anomalous development of the valve

Pulmonary atresia was present in 3 of the 4 cases of atrial venous valve in the fourth case the tricuspid valve opened into a single ventricle[22] Since formation of the pulmonary valve normally antedates resorption of the venous valves, a primary pulmonary atresia may have affected resorption of the valve On the other hand it is conceivable that the pulmonary valve was normally formed but became fused at a later date because of reduced blood flow

A causal relationship between the maldevelopment of the right heart and the multiple communications between the coronary arteries and right ventricle seems probable but the mechanism is unclear The majority of examples of coronary ventricular communications occur as isolated anomalies[6,23] but those that are seen in conjunction with malformations of the right heart are strikingly similar In the literature there are 10 postmortem cases in which anomalies of the right heart were associated with coronary artery–right ventricle fistulas, excluding cases in which a single coronary artery arose from above or just below the pulmonary valve. These 10 cases together with the present one, are summarized in Table I In 10 of the 11 cases there was atresia of the conus and/or pulmonary valve and in one there was pulmonary stenosis. The tricuspid valve was small or deformed in 9 in one it was normal and in the other the valve was not described Right ventricular hypertrophy was constant, whereas the ventricular cavity was often very small

Edwards[6] has considered coronary ventricular communications in such hearts to be secondary malformations, which result from increased intraventricular pressure The right ventricle becomes a closed chamber during systole, when the ventricular septum is intact, the pulmonary valve is atretic and the tricuspid valve is competent the high pressure thus created favors persistence of normal communications between embryonic sinusoids and coronary arteries. Although this explanation seems to fit well some of the hearts described in Table I many of them do not fulfill the criteria for trapping of blood in systole Of the 11 cases, 1 had a single ventricle 2 had a ventricular septal defect 1 had pulmonic stenosis and not atresia and in at least 3 the tricuspid valve could be considered to be incompetent

Muir[11] and Guldici and Becu[8] have questioned Edwards theory of pathogenesis of coronary ventricular communi-

cations associated with other cardiac malformations. The latter authors, who believe that the malformation is primary state that at the stage of development in which normal embryonic coronary ventricular communications are disappearing the ventricular septum is still partly open. Furthermore the majority of pulmonary or aortic atresias show no such fistulas.

Grant[7] considered that maldevelopment of the anterior cardiac tube was responsible in his case for both the pulmonary atresia and the persistence of intertrabecular spaces which communicate with the coronary artery. The latter spaces, which reach the epicardium in the embryo are normally reduced to capillaries by the growth of compact myocardium. He explained the aneurysm of the coronary artery but not the coronary ventricular communication as probably being secondary to increased intraventricular pressure of blood in the conus region.

Our review of cases has led us to believe that factors other than elevated intraventricular pressure may be required to explain the origin of coronary ventricular communications. If an initial defect in cortical myocardial expansion occurs, then embryonic channels would persist and retain their connection with the coronary vessels. After septation of the heart is completed even mild differences in pressure would become important.

Summary

An unusual malformation of the heart in a newborn infant is described consisting of persistent venous valves in the right atrium, hypoplasia of the tricuspid valve pulmonary atresia, and multiple coronary artery ventricular communications with the right ventricle. Coronary flow to the right heart was shunted through the right ventricle and focal necrosis was seen in the right ventricular myocardium. The pertinent literature is reviewed and the pathogenesis of the malformation is discussed

Addendum

Since this manuscript was submitted for publication a valuable review and classification of various types of right atrial valves has appeared [17]

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Thymolipoma simulating cardiomegaly: Opacification of the tumor by cineangiocardiography

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Thymolipoma is a rare benign tumor consisting of fat and thymic tissue. This tumor has been the subject of sporadic case reports[1-4] in the English literature since the articles of Hall[5] and Schanker and Hodge in 1949 It is the purpose of this paper to report the case of a patient who presented with asymptomatic cardiomegaly which was shown to be due to a thymolipoma To our knowledge this is the first patient with this tumor in whom cardiac catheterization has been performed and the tumor opacified by cineangiocardiography

Case report

D W (Hosp #459910 USNH Portsmouth Va.) was 4-year-old white boy who was seen in cardiac consultation on June 12 1961 for evaluation of an enlarged cardiac silhouette which was detected on a routine initial chest roentgenogram The patient was asymptomatic from a cardiopulmonary standpoint. He was the product of a normal full term pregnancy with spontaneous delivery and no known neonatal distress. His growth and development were normal, and he was considered to be extremely bright active and alert. The patient had the usual childhood diseases, without complications. There was no history of heart murmur cyanosis, squatting, migratory polyarthritis, pneumonia, cardiac arrhythmia or decompensation. He had frequent infections of the upper respiratory tract but these responded quickly to symptomatic measures and only occasionally required antibiotics. His only significant past medical history was that of partial distal urethral obstruction secondary to congenital stricture without complicating infections of the urinary tract. The only previous roentgenograms consisted of intravenous urograms.

The patient had one sibling 5 months old, who was living and well and whose chest x-ray film was normal. There was no family history of congenital or acquired heart disease.

On physical examination the patient was a very active well-developed and well-nourished white male child in no distress. He was in the eighty-fifth percentile according to height and weight. The blood pressure was 84/50 mm. Hg in the arms and 115/80 mm. Hg in the legs. There was no paradox or alternans. Examination of the skin, head eyes, ears, nose and throat was within normal limits, except for bilaterally enlarged tonsils. Both carotid arteries were palpable full, and equal. There was no cervical venous distention or abnormal venous pulsations. The thyroid was not palpable. The lungs were clear to percussion and auscultation. There was no demonstrable developmental abnormality of the bony rib cage A normally active precordium without shocks, thrills lifts, or heaves was present The point of maximal impulse was not visible or palpable. The heart was not definitely enlarged to percussion Sinus arrhythmia was present The second sound was loudest at the base and was best heard in the second left intercostal space Two components of the second sound were audible with physiologic splitting of the second sound. No significant murmur

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rub, gallop or extracardiac sound was audible. The liver and spleen were not palpable. All peripheral pulses were palpable, full and equal. There was no clubbing, cyanosis, or edema.

The electrocardiogram revealed sinus arrhythmia with a clockwise QRS loop in the frontal plane and a mean QRS axis of +60 degrees. The mean T vector was at +30 degrees and directed slightly posteriorly. This electrocardiogram was considered to be within normal limits.

The posteroanterior and lateral chest films are shown in Fig. 1. In the posteroanterior projection there was generalized enlargement of the cardiac silhouette with a triangular configuration and no evident specific or selective chamber enlargement. The transverse cardiothoracic ratio measured 12.5/18 centimeters. The aortic knob was well identified, appeared to be normal in size and configuration and descended on the left. In the lateral view the heart did not appear to be significantly enlarged; however, there was some decrease in the anterior clear space. In the right and left anterior oblique views (not shown) there was both anterior and posterior encroachment by the cardiac silhouette.

Fluoroscopy confirmed the roentgenographic findings and revealed a generalized decrease in cardiac pulsations.

The initial impression was that of pericardial disease with the possibility of a diffuse pericardial cyst. In view of his entirely asymptomatic state it was agreed to follow him for a short period of time with serial chest films and to perform further diagnostic studies in the near future. He was seen at monthly intervals with no change in his symptoms, physical examination, or chest x-ray film.

On J 9, 1962, approximately 6 months after his first visit to the Cardiac Clinic, the patient was studied by catheterization of the right side of the heart and cineangiocardiography. All pressures and oxygen data were within normal limits (Table I). Indicator-dilution curves, performed with the in-

Table I. Data from catheterization of the right side of the heart

Site	Pressure (mm Hg)		O_2 Saturation (vol %)
	S/D*	Mean	
Superior vena cava		0	10.86 (75%)
Inferior vena cava		0	—
Right atrium (mid)		+2 to −2	11.01 (76%)
Right ventricle	27/3	—	—
Main pulmonary artery	24/8	18	10.43 (72%)
Right brachial artery	84/45	60	14.08 (97%)
Capacity	—	—	14.49 (100%)

*Systolic/diastolic.





Fig. 1. Posteroanterior (above) and lateral (below) preoperative chest roentgenograms.

jection of indocyanine green into the superior vena cava and pulmonary artery with sampling from the right femoral artery, showed normal appearance times and recirculation, with no evidence of right-to-left or left-to-right shunting. Cineangiocardiography was performed with the injection of 20 c.c. of contrast medium (Diodrast) into the upper superior vena cava, using the Gidlund power syringe. After the cineangiocardiogram was completed, persistent contrast medium was noted fluoroscopically in the paracardiac area, without evidence of cardiac tamponade. Approximately 15 minutes later the contrast material had cleared from this area.

The cineangiocardiogram revealed rapid entry of contrast material into multiple discrete vascular



Fig. [illegible] Fig. 3 (center). Fig. 4 (bottom). (For legend see bottom of opposite page.)



Fig. 5 The surgically removed paracardiac mass.

channels in paracardiac mass (Fig. 2). Most of these vessels were seen on the right side of the heart however few smaller vascular channels were noted on the left side of the cardiac silhouette (Fig. 3). Subsequent frames revealed progressive homogeneous opacification of paracardiac mass which was more dense on the right than on the left side (Fig. 3). The superior vena cava, right atrium, right ventricle, pulmonary artery left atrium, left ventricle and aorta opacified normally. The heart moved freely within this extracardiac mass, and there appeared to be no restrictive or constrictive impairment of its emptying or filling. There was no evidence of valvular obstruction or abnormal intracardiac shunting of the contrast media. Fig. 4 was taken from frame late in the cineangiocardiogram and shows normal-sized heart silhouetted against the surrounding opacified paracardiac mass, with some of the contrast material still visible in discrete channels. Definite sites of vascular inflow and outflow to this mass could not be delineated. A presumptive preoperative diagnosis of pericardial hemangioma was made and the patient was scheduled for exploratory thoracotomy.

On Feb. 21 1962 the patient underwent exploratory mediastinotomy through median sternal splitting incision. When the mediastinal structures were exposed, a tumor mass (Fig. 5) was identified and noted to be extrapericardial. It was well localized, encapsulated, and separated from the pericardium and surrounding tissues by thin layer of gossamer tissue. In addition to its vascular attachment and blunt-like pedicle in the superior anterior mediastinum in the area normally occupied by the thymus. The tumor mass was easily removed, and its small and medium-sized feeder vessels were easily ligated. Positive identification of all the vascular channels visualized in the cineangiocardiogram was not possible however those demonstrated in Figs. 2 and 3 were well seen on the posterior surface of the tumor mass. The patient withstood the procedure without difficulty and had smooth postoperative course. Since discharge on March 2, 1962 he has been re-evaluated on several occasions. The findings by physical examination has been normal, and roentgenographically he has normal cardiac silhouette.

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Fig. 6 Representative microscopic section of the tumor showing intertwining fatty tissue with lymphoid follicles and Hassall corpuscles (×100).

Fig. 2 A single frame from the cineangiocardiogram taken immediately after the injection of contrast medium, showing opacification of multiple, discrete vascular channels predominantly on the right side within the paracardiac mass.

Fig. 3 A single frame taken a few seconds after that seen in Fig. 2 showing filling of vessels to the right and left of the silhouette, along with progressive homogeneous opacification of the paracardiac mass, which is more dense on the right. The contrast medium is also seen in the superior vena cava and chambers of the right side of the heart.

Fig. 4 A single frame taken at the end of the cineangiocardiogram showing normal-sized heart silhouetted against the surrounding paracardiac mass, with some discrete vascular channels still visible.

Pathologically the right half of the tumor was very firm, nodular, slightly irregular, and dark brown to red in color. The left half had a softer, smoother texture and was [illegible] yellowish in color. Sectioning revealed multiple soft, brownish-yellow areas throughout the tumor. Fig. 6 shows a representative microscopic section. Histologically, the tumor was composed of intertwining and interlocking areas of fatty tissue with lymphoid follicles and Hassall corpuscles compatible with thymic tissue, thus fitting the description of a thymolipoma.

Discussion

To date 13 well-documented cases of thymolipoma have been reported in the English literature[2-14]; 2 additional cases[15,16] probably represent this tumor but are reported as thymomas, and another case[17] is reported as a lipoma. The present patient is the youngest one with a thymolipoma to be reported on in the literature, and his is the first case in which opacification of the tumor has been demonstrated by cineangiocardiography or studied by cardiac catheterization. Four previous cases[12,13,14] were studied by angiocardiography without opacification of the tumor.

Several clinical points in regard to thymolipomas are worth noting. (1) The majority of patients with this neoplasm are asymptomatic; when symptoms are present, they are due primarily to the mechanical effects of the tumor. (2) All thymolipomas are benign and have been cured by operative removal. (3) The varied roentgenographic manifestations of this anterior mediastinal tumor have been emphasized previously.[14] (4) In no case have there been associated symptoms of myasthenia gravis or other clinical syndromes peculiar to thymic tumors. (5) In view of a recent report by Griffith and associates, which demonstrated involution of the thymic gland with adrenal steroids in infants, it would have been of interest had steroids been used in our patient and the response of the thymolipoma observed.

Although three reviews[21] of thymic neoplasms fail to mention thymolipoma, this tumor must now be included in the differential diagnosis of all masses in this anatomic location. In no reported case, including the present one, was a correct preoperative diagnosis made. A number and variety of diagnostic tests have been proposed, and this report emphasizes the value of cineangiocardiography.

SUMMARY. An asymptomatic 4-year-old white boy who presented with cardiomegaly was shown to have a thymolipoma with opacification of the tumor mass by cineangiocardiography.

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Aortic insufficiency secondary to spontaneous rupture of a fenestrated leaflet

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It is well appreciated that rheumatic heart disease is the most common cause of aortic insufficiency. However, it is unusual for a patient with severe rheumatic aortic insufficiency to survive past the fifth decade. Thus, if one is confronted with an elderly patient with severe aortic insufficiency, other etiological possibilities must be considered.

Among the more unusual causes is spontaneous rupture of a fenestrated valve leaflet. It seemed appropriate to document an example of this uncommon entity. This presentation affords an opportunity to discuss factors which contribute to spontaneous rupture of fenestrated leaflets.

Case report

A. D., a 67-year-old Negro woman, was admitted to the Georgetown University Medical Division of the District of Columbia General Hospital on July 18, 1962, because of increasing symptoms of biventricular congestive heart failure.

She had a 16-year history of hypertension. Four years prior to her death, left ventricular failure occurred. At that time, her blood pressure was 194/100 mm. Hg, and a Grade 3/6 murmur of aortic insufficiency was heard. The etiology of this murmur was undetermined since there was no history of syphilis, rheumatic fever, chest trauma, or endocarditis. Over the next 3 years the usual treatment for congestive heart failure was sufficient to maintain cardiac compensation. During this interval the diastolic blood pressure fell gradually to 60 mm. Hg. During the year before her final hospitalization she sustained repeated bouts of biventricular failure.

Physical examination disclosed a thin, anxious, orthopneic, elderly woman. The blood pressure was 180/60 mm. Hg. The jugular venous pressure was elevated. There was a bisferiens carotid pulse. The chest was hyperresonant throughout, with diminished breath sounds. The point of maximal cardiac impulse was located in the fifth intercostal space at the anterior axillary line, and was sustained in a manner typical of left ventricular hypertrophy. On auscultation, the first heart sound was diminished in intensity. Both atrial and ventricular diastolic gallops were present. A Grade 2/6 aortic ejection murmur and a Grade 4/6 diastolic blow were heard best along the left sternal border. Hepatomegaly and peripheral edema were present.

Serologic tests for syphilis were persistently negative. The electrocardiogram was consistent with left ventricular hypertrophy and strain. There was left axis deviation. The P-R interval was 0.21 second. The chest roentgenogram is illustrated in Fig. 1.

The congestive heart failure proved to be intractable, and she died on the eighth hospital day.

Autopsy. At autopsy the heart weighed 800 grams. Cardiomegaly was due principally to hyper

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Fig 1 Posteroanterior roentgenogram showing marked cardiomegaly and bilateral pulmonary congestion The blunting of the right costophrenic angle is consistent with right pleural effusion.

trophy of the left ventricular wall which measured 1.5 cm The pericardial surfaces of the heart were normal

The right and left anterior (coronary) aortic cusps were fenestrated The valvular endocardium which formed the superior rim of one of the fenestrations of the left anterior cusp was disrupted 0.1 cm from the commissure (Fig 2) The endocardial tags that remained were thin smooth glistening, and gross separation of this margin of the valve resulted in lack of lateral support which allowed the cusp to sag The new free margin of the deformed cusp was below the normal line of closure The failure of proper apposition of this deformed cusp resulted in insufficient aortic valve Further evidence of insufficiency of this cusp was endocardial sclerosis which involved the outflow tract directly beneath the altered cusp The aortic ring was not dilated It measured 8 cm in circumference There was no suggestion of recent or old bacterial endocarditis. There were no other valvular abnormalities

The remainder of the autopsy reflected severe congestive heart failure which was manifested by chronic passive congestion of the lungs, liver and spleen.

Discussion

It is likely that rupture of the aortic cusp resulted in the sudden appearance of congestive heart failure 4 years prior to death During this time the gradual fall in the diastolic blood pressure may have been the consequence of progressive prolapse of the ruptured leaflet

Four other cases of spontaneous rupture of fenestrated aortic cusps have been reported in the English literature Matthews and Darville[2] reported the case of a 67 year-old man with hypertension and aortic insufficiency in whom there was a sudden change of a Grade 4/6 diastolic murmur to a Grade 6/6 diastolic blowing murmur Although blood cultures were negative the patient was treated for bacterial endocarditis. Autopsy showed multiple aortic and pulmonary valve fenestrations and rupture of an aortic cusp. Proudfit and McCormack[3] described the case of a 56-year-old hypertensive man who abruptly developed a diastolic murmur accompanied by left ventricular failure. He improved with medical treatment but died unexpectedly in his sleep 14 months later An autopsy revealed a fenestration of the aortic valve with rupture at the point of attachment to the cusp. There was no evidence of endocarditis in these 2 cases or in the present case report. Two cases of rupture of fenestrated aortic valves in patients with syphilitic aortitis have also been documented

An analysis of the reported cases including our own revealed factors which may predispose to rupture of a fenestrated aortic valve It has been postulated that the fenestrated leaflet is weakened because of the loss of valvular substance[4] A description of the fenestrated cusp may clarify this concept.

Fenestrations are perforations of the semilunar valves which lie close to the free edge of the valve cusp near its insertion into the annulus (Fig 3) Because of this marginal location above the line of closure of the leaflets fenestrations alone are rarely a cause of regurgitation[5-] However they do result in a loss of valve substance in such fashion that the outer margin of the cusp is supported by only a thread like strand. In all reported cases of spontaneous rupture it was the disruption of this remaining strand which resulted in the valvular insufficiency

It is surprising that this sequence of events does not occur more frequently because fenestrations of the semilunar valves are common Fox reported that fenestrated semilunar valves were found in 82 per cent of 300 unselected autopsies.

Friedman and Hathaway[4] found valvular fenestrations in 72 per cent of the 347 cases which were reviewed. Their presence may frequently be overlooked or considered to be unimportant by the prosector.

The fenestrated aortic valve may be ruptured by the additional stress of the high diastolic closing pressure of hypertension. Three of the patients who were reported to have spontaneous rupture of a fenestrated valve had a background of hypertension.

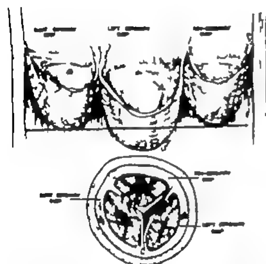


Fig. 2. Drawing of the aortic cusps reproduced from sketch made at autopsy. The arrows point to the separation of the superior rim of the left coronary cusps. The lack of this lateral support allowed this cusp to sag. The bottom figure illustrates that the failure of proper apposition of this cusp with the other two cusps resulted in aortic insufficiency.



Fig. 3. Drawing of fenestrated aortic valve, a common autopsy finding. Aortic insufficiency does not usually occur as a result of fenestrations, since the line of valve closure is below the fenestrations. The arrow points to the site in which rupture occurred in our case.

Dilatation of the aortic ring in syphilitic aortitis induces secondary valvular changes. Often the valvular leaflet is stretched to its maximal length. The line of closure is elevated from a point nearly midway in the valve substance to its outer margin. Therefore, more strain is placed on the free edge of the valve. In a fenestrated cusp this leaflet margin, often a thin strand of tissue, may rupture. This apparently occurred in the 2 patients reported on by Carroll.

It is of interest that spontaneous rupture of a fenestrated pulmonary valve has not been described even though fenestrations occur as often in the pulmonary as in the aortic valves. This may be a reflection of the lesser degree of stress to which these valves are subjected.

Summary

Spontaneous rupture of a fenestrated valve leaflet is one of the unusual causes of severe aortic insufficiency.

A case is presented of an elderly woman with severe aortic insufficiency who was shown at autopsy to have rupture of a fenestrated valve leaflet.

A review of the English literature revealed 4 other cases of spontaneous rupture of a fenestrated aortic valve leaflet. In these cases, as in ours, the patient had either hypertension or syphilitic aortitis in addition to the valvular fenestrations.

It would appear that the weakened fenestrated valve in conjunction with the additional stress imposed on the aortic valve by systemic hypertension or syphilitic aortitis are factors which predispose to spontaneous rupture.

Addendum

Since this manuscript was submitted for publication, Levy and associates have described another instance of spontaneous rupture of a fenestrated aortic valve. In their case, aneurysmal dilatation of the ascending aorta due to cystic medial necrosis resulted in stretching and tension of the cusps with consequent rupture of the free margin of the left cusp.

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Special report

Dental procedures of interest to the physician in the management of patients with cardiovascular disease

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Physicians are frequently called upon by dentists to determine whether it is permissive to perform certain dental procedures on patients who are suffering from various cardiovascular diseases. Most physicians are usually aware of the problem of hemorrhage and bacteremia which results from the extraction or removal of teeth but the extent of trauma that is associated with this well known procedure needs elucidation For example the extraction of numerous loose teeth may be less traumatic than the removal of a single tooth especially one that is encased in bone such as an impacted tooth Both operations are classified as oral surgery but there is a great difference in the degree of trauma associated with each

Other less well known dental manipulative procedures can cause a greater amount of hemorrhage and bacteremia than does the removal of some teeth Moreover there are some extensive nonsurgical procedures that also create problems with the use of local anesthetic and vasoconstricting agents.

The following description of dental procedures will help the physician in understanding the nature of the dental problem Thus he will be able to give maximum protection to the patient who is suffering from cardiovascular disease.

Local anesthesia

The induction of local anesthesia is a very common procedure that is used quite extensively not only for oral surgery but also in periodontics (treatment of the gums) endodontics (root canal therapy) operative dentistry (fillings) and crown and bridge procedures (oral reconstruction or mouth rehabilitation) It has been estimated that local anesthesia is used five times more often in dental procedures other than exodontia and oral surgery Although some of the more recent local anesthetic agents may be effective without the use of vasoconstrictors in oral surgery they are not completely effective in other dental procedures. In order to achieve total and complete anesthesia which is essential in patients with cardiovascular disease vasoconstrictors in approved amounts must be added to the local anesthetics. If the anesthesia is not profound the stressful situation will cause the physiologic liberation of more epinephrine by the adrenals than may be present in the anesthetic agent. Care should be exercised by injecting slowly using the aspiration technique in order to prevent any of the anesthetic and vasoconstrictor from entering into the circulation In patients with ischemic heart conditions the presence of epinephrine may create a problem. Perhaps the

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ubstitution of other vasoconstrictors may circumvent the problem.

In patients on anticoagulant therapy the use of local anesthesia does not produce any increase in submucosal hemorrhage. This may be attributed to the use of a fine-gauge needle and the presence of vasoconstrictors.

The type of anesthesia to be used in patients with valvular heart damage, particularly in those with a history of rheumatic fever, has been debated quite at length by the proponents of local and general anesthesia. The protagonists of general anesthesia claim that puncture of the injection site with a local anesthetic may introduce microorganisms into the tissues and perhaps into the blood stream before any dental manipulation is performed. This danger can be eliminated by sterilization of the site of injection and by the use of an aspirating syringe. Under general anesthesia this complication does not occur.

In studying the problem of bacteremia we have not been able to observe any relationship between the procedure of injection and the bacteremia. In over 700 cases in which blood for culturing was taken preoperatively, immediately after the injection of a local anesthetic, we found only 4 positive blood cultures, an incidence of a little more than one-half per cent. This small incidence may possibly be attributed to contamination after venipuncture. It is doubtful whether a sufficient number of bacteria could be introduced through the puncture site to produce detectable bacteremia.

It has been claimed that the use of a local anesthetic with epinephrine or other vasoconstricting agents compresses the capillaries, thereby curtailing the dissemination of the microorganisms into the blood stream. The concentration of the vasoconstrictors present in the local anesthetics contracts the capillaries only at the depot site to maintain the anesthetic so that it can exercise its function. The vasoconstrictors do not necessarily compress the capillaries at the site of extraction.

Studies have shown conclusively that the addition of epinephrine to the anesthetic agent plays no role in curtailing the incidence of bacteremia. Without the use of epinephrine, cultured samples of blood displayed an incidence of 83 per cent positive, whereas with the addition of epinephrine 87 per cent of the cultures were positive.[9]

It is the authors' opinion that, in addition to other considerations, local anesthesia is preferable because, with the patient under local anesthesia, the operator produces less trauma during the manipulative procedures, whereas with the patient under general anesthesia the operator may use a more forceful manipulation. This factor of trauma plays an all-important role in transient bacteremia.

Exodontia

Most physicians are aware that the common problem of the dentist is exodontia or removal of teeth. The trauma of extraction, with its forceful manipulation, is one of the most important factors in producing bacteremia. Laceration of the venules and capillaries creates the entrance through which bacteria enter the blood stream. The number of teeth extracted at one session is often related to the degree of trauma.

Almost all investigators agree on the relationship of trauma to bacteremia. Some, however, find this relationship only in regard to the number of teeth extracted at a single time. One must bear in mind that it is not always the number of teeth extracted that causes the extensive operative trauma. For example, in the case of removal of seven or ten teeth, if there is extensive alveolar bone resorption and the teeth are quite loose, fewer blood vessels are opened comparatively, and there is less likelihood of detectable bacteremia. Cultured samples of blood often prove to be negative for growth under such conditions. On the other hand, the process of extraction of one or two firm teeth which have a great deal of alveolar bone surrounding them can produce a greater amount of trauma, with detectable bacteremia and hemorrhage. There are a greater number of lacerated blood vessels per unit of tooth area around one or two teeth under such circumstances than in the case of seven or ten loose teeth.

Heavy trauma due to forceful rocking of the tooth from side to side invariably pro-

duces a greater dispersion of bacteria into the blood stream. Milder trauma produces a lesser dispersion. It should be emphasized that bacteremia occurs 100 per cent of the time after any oral surgical procedure, depending on the size of the sample of blood taken for culturing. We were able to increase the incidence of bacteremia from 54 to 88 per cent by increasing the size of the sample of blood from 4 to 24 ml.

In our studies we were able to demonstrate a definite gradient relationship between the trauma of extraction and the incidence of bacteremia. Heavy trauma produced an incidence of 93 per cent positive blood cultures, whereas mild trauma produced an incidence of 68 per cent. We were also able to demonstrate that the removal of a single tooth produced a lower incidence of bacteremia (51.5 per cent) than did multiple extractions (84.9 per cent) (see Table I).

In addition, we were also able to observe that hemorrhage occurred more readily in cases of heavy trauma and that heavy trauma was less prevalent in the younger age group (ages 16 to 24 years).

The factor of trauma has the effect of controlling the amount of the inoculum. This is an important consideration since the amount of the inoculum is one of the factors related to the establishment of disease. Therefore, it appears that the incidence of bacteremia and the possibility of the development of subacute bacterial endocarditis can be minimized by limiting the number of teeth to be extracted in patients with valvular heart disease. Curtailment of the number of bacteria which enter the circulation is a more effective means of prevention than dependence on antibiotics. In addition, we have been able to demonstrate that antibiotic therapy is more effective in cases of *mild trauma*.

A number of investigators have intimated that the extraction of teeth with periapical abscesses can cause bacteremia. In an evaluation of our results, we found no increase in the incidence of bacteremia in cases of periapically involved teeth as compared with cases in which the teeth were free of periapical complication as visualized on the roentgenograms. It should be mentioned that not all areas of apical rarefaction are due *to infection*. Areas of radiolucency can manifest themselves after sterile necrosis of the pulp tissue. Moreover, it has been shown that the areas of rarefaction are comprised of granulomatous tissue in which the bacteria are killed. Bacteriologic cultures of these areas have demonstrated that few if any bacteria survive in this granulomatous tissue.[8]

The mere presence of the apical granuloma does not cause bacteremia. However, more hemorrhage can be anticipated when extractions are performed by traumatizing the granulation or inflammed tissue around the tooth.

It has been shown quite conclusively that hemorrhage after oral surgery procedures is not a serious problem in patients on anticoagulant therapy. If patients are on anticoagulants, individual adjustments of prothrombin time should be made selectively.

Periodontia

Procedures other than exodontia can produce hemorrhage and bacteremia as a result of manipulation, i.e., periodontic procedures. Periodontic procedures are performed to curtail and eliminate gingival inflammation, to prevent resorption of alveolar bone, and to maintain the normal integrity and architecture of the gum tissue. Thus, the individual's natural teeth can be retained for a longer period of time. In the process of eliminating gingival disease, different procedures are used and the resultant hemorrhage and bacteremia are dependent upon the trauma of the procedures.

In our studies on bacteremia after various periodontal procedures, scaling the teeth by removing the tartar or calculus with the use of scaling instruments introduced subgingivally produced a lower incidence of bacteremia than did deep scaling. In deep scaling, the scaler is introduced more subgingivally, thus opening many more blood vessels than does the superficial scaling procedure. Scaling is done to remove calcareous deposits or calculus which collects around the necks of the teeth at the gum line. These deposits grow downward, pushing away the gum. As the deposits increase, the gum becomes inflamed as a result of the mechanical irritation. It is essential that this irritant

Table I. Incidence of bacteremia in exodontic, periodontic, and endodontic manipulation

Procedure	Number of cases	Positive cultures: Immediately after manipulation		Positive cultures: 10 Minutes after manipulation	
		Number	Per cent	Number	Per cent
Multiple extraction	93	79	84.9	41	44.0
Heavy trauma	61	57	93.4	30	49.2
Mild trauma	32	22	68.7	11	34.3
Single extraction	33	17	51.5	8	24.2
Gingivectomy	12	10	83.3	3	25.0
Deep scaling	15	8	53.3	2	13.3
Light scaling	20	6	30.0	1	5.0
Group A (within root canal)	50	0	0.0	0	0.0
Group B (beyond root canal)	48	15	31.2	0	0.0

be removed in order to eliminate gingival inflammation.

Gingivectomy is another periodontic procedure that is used to eliminate gingival inflammation. This is a more extensive and traumatic procedure than the aforementioned procedures. With this procedure, hemorrhage is more extensive and the incidence of bacteremia is as high as with the heavy trauma of extraction. The amount of trauma, with the ensuing hemorrhage and bacteremia, is dependent upon the clinical procedure. For example, brushing of the teeth, scaling, curettage, gingivoplasty, gingivectomy, and other forms of periodontal surgery all differ in the degree of trauma which they produce, and this difference affects the resultant bacteremia. Positive cultures of blood have been reported after brushing of the teeth, and the chewing of various foods or a resistant mass. If gingival inflammation is present, any trauma, even if it is slight, can produce bleeding and thus establish a portal of entry for the bacteria into the blood stream (see Table I).

It is quite obvious that patients with periodontal disease who suffer from rheumatic or congenital heart disease can potentially develop subacute bacterial endocarditis more readily than patients with other inflammatory processes, for example, periapical inflammation. Prevention of periodontal disease in such patients is essential. If periodontal treatment or even a prophylaxis or cleaning of the teeth is to be done, manipulation should be kept to a minimum. Clinical judgment should dictate what procedure to institute in order to minimize the factor of trauma.

Endodontia

Another procedure that exposes patients to manipulative trauma is endodontia or root canal therapy. In this procedure the inflamed pulp, as a result of carious involvement, is removed from within the root canal by means of fine, delicate instruments. As a result of this therapy, teeth need not be removed; the root canal is cleansed of the organic pulp tissue, sterilized, and filled. Quite frequently, when the pulp of the tooth is necrotic and/or if an apical abscess is present, a local anesthetic is not necessary. In addition, hemorrhage is not a factor in this procedure. This fact has even been observed in patients suffering from hemophilia who were in need of endodontic therapy.

Of all the dental manipulative procedures, this is the least likely to result in the complications of hemorrhage and

bacteremia because the area of manipulation is small and limited. Comparatively, the number of capillaries and blood vessels that are open to the entry of bacteria is certainly much smaller than in the case of the extraction of teeth or any periodontal manipulation. Although the blood vessels and capillaries of the vital pulp may be rich and extensive within the tooth, the number of venules and veins that exit from the canal of the tooth are limited in number, usually from one to ten. The pulp of the tooth has a very much limited collateral circulation. Thus, the bacteria are confined within the pulp tissue and do not readily gain entry into the circulation. Moreover, endodontic procedures are done by isolating the involved tooth under the rubber dam by means of a surgically clean technique. In addition, the root canals are filled only after a negative bacteriologic culture is obtained. Thus, the possibility of contamination and bacterial entry is further reduced. However, surgical endodontics which necessitates the resection of the apex of the tooth with the attached granuloma exposes the patients to complications of hemorrhage and bacteremia.

Studies of bacteremia after conservative endodontic procedures revealed that, in the manipulation of pulp removal and cleansing performed on vital teeth or nonvital teeth with apical abscesses, no detectable bacteremia occurred if the instrumentation was confined within the root canal. However, if the mechanical cleansing was performed by pushing the instruments beyond the apex of the tooth into the surrounding bone marrow spaces, positive cultures of blood were recovered in 31 per cent of the cases[8] (see Table I).

Other endodontic procedures, such as pulp capping and pulpotomy, which are less traumatic in nature than pulpectomy, have also been studied.[12] Here, too, no detectable bacteremia was reported.

The treatment of an acute alveolar abscess or apical periodontitis can be a factor of great concern in the development of bacteremia due to the more virulent microorganisms. Under such circumstances, it is essential that drainage be established. Drainage can be established through the root canal. Whenever possible, it is a much safer procedure to establish drainage by opening the root canal than by ordinary surgical incision.

Other procedures

Procedures such as filling of the teeth, fabrication of crowns, orthodontic manipulation, and the taking of impressions for dentures should cause no concern, since none of these cause any hemorrhage or bacteremia. A few cases of bacteremia[13] and subacute bacterial endocarditis have been reported after the filling of teeth. This occurrence is questionable, and most likely was the result of an associated periodontal condition. Harvey and Capone[14] reported the occurrence of two cases of subacute bacterial endocarditis 5 months after the filling of teeth. Since patients visit the dentist routinely, the disease may have developed as a factor of coincidence. Likewise, one might develop subacute bacterial endocarditis after a tonsorial manipulation such as a haircut or after manicuring of the fingernails, which also are routine procedures. Although it has been shown experimentally in animals that bacteria can get through the dentin in very deep preparations, especially when the cavities are subjected to pressure,[15] it is questionable whether enough bacteria can get into the blood stream to produce detectable bacteremia.

However, some consideration should be given to changes due to posture which may occur in patients on certain antihypertensive drugs when these patients are placed in a reclined position in the dental chair. The sudden change from the reclining position when the patient is dismissed may result in an episode of hypotension or syncope. Moreover, the stress associated with dental procedures, especially those of long duration, such as mouth reconstruction or oral rehabilitation, may also precipitate these reactions.

Summary

In summary, it appears that exodontic, periodontic, and certain endodontic procedures are of major concern. Clinical procedures can be modified to reduce the hazard of hemorrhage and bacteremia by extracting one tooth at a time or by treating small segments of periodontally involved teeth. Whenever possible, endo-

dontics should be performed rather than exodontics. Moreover clinical judgment should dictate what procedures to adopt. Complete and profound local anesthesia is essential in patients with cardiovascular disease.

Fillings, restorative prostheses, and orthodontic procedures are of little concern in the absence of periodontal disease or gum inflammation.

The length of each dental appointment should be as short as possible.

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Review

The nonvascular metabolic myocardial vulnerability factor in "coronary heart disease"

Fundamentals of pathogenesis, treatment and prevention

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Expediency of verbal communication concerning complex issues necessitates the use of brief stereotyped expressions which are intended to broadly characterize the cardinal features of the subject in question without any direct reference to points considered to be of secondary significance. Such linguistic simplifications, if perpetuated, are liable to distract attention from momentous changes within their subject area, and thus to hamper expansion of its understanding.

The term "coronary heart disease" is a case in point, with far-reaching implications concerning questions of pathogenesis, therapy, prevention, insurance, and the planning of research projects.

Early descriptions of the clinical signs and anatomic findings connected with coronary thrombosis were published by Hammer (1878), Leyden (1884), Huchard (1903), Obrastzov and Strashesko (1910)[1] and others but aroused only relatively little attention until the classic work of J. B. Herrick (1912) brought the importance of coronary occlusion sharply into focus for the medical world. The impact of this landslide in clinical cardiology, enhanced by Keefer's and Resnik's (1928)[2] emphasis on the role of myocardial oxygen want in the anginal syndrome, initiated an era of rigidly mechanistic thinking. For decades nearly all degenerative morphologic and associated functional disturbances of the heart muscle were attributed to impairments of coronary blood flow, ranging from hypothetical coronary spasms to sclerotic stenosis and thrombotic occlusion.

The presence of anatomic vascular lesions, either in unquestionable topical and causal relation to myocardial infarcts, or at least at some distance from injured areas, could be ascertained in the vast majority of instances of degenerative myocardial disease, especially of the left ventricle.[3-6] In view of these impressive autoptic findings and of their usual coexistence with the clinical syndrome of angina pectoris and myocardial infarction, it has become common usage to designate this category of syndromes as "coronary heart disease," "coronary artery disease," "coronary disease," or, in layman's language, even simply as "a coronary." Thus, the accepted terminology completely disregards the frequently decisive participation of primarily noncoronary pathogenic mechanisms which determine the degree of vulnerability of the heart muscle to coronary impairments. Furthermore, the terms "coronary thrombosis" and "coronary occlusion" are often used glibly without any proof of existing vascular obstruction.

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Unfortunately, except in cases of massive transmural infarction, the clinical diagnostician is practically always confined to guesswork and to conventional prejudice, since not even the modern methods of coronary catheterization and coronary angiography can be generally expected to provide conclusive information in the individual case.[illegible] Data on total coronary flow and on the oxygen saturation of the coronary sinus blood do not clearly reflect the presence and location of circumscribed areas of anoxia in the myocardium nor their causative mechanism. Radiographically discernible abnormalities of coronary circulation do not make possible a differentiation between those portions of the heart muscle which are adequately supplied by collateral and others which are not. Old occlusion of coronary arteries in patients without a history of [illegible] and without autopsic signs of myocardial damage have been observed (Blumgart and associates and others) in relatively large numbers.

Under these bewildering circumstances the routine application of the term "coronary heart disease" (often with undue emphasis on the word "coronary") represents a convenient but easily misleading escape from an unwelcome dilemma by ignoring those physiopathologic and metabolic factors which are co-responsible for the degree of myocardial vulnerability, and thereby for the prognosis in the individual case as well as for the general pathogenesis of degenerative heart disease.

A. Absence of coronary occlusion and stenosis in cases of "coronary heart disease"

Disseminated necrotic and fibrotic foci and "zonal infarctions" of varying sizes are frequently found at autopsy without any obstruction of the corresponding regional coronary branches. They are usually located in the subendocardial layers of the left ventricle, in papillary muscles, and the ventricular septum.[illegible] Blumgart and associates observed acute myocardial infarctions without acute coronary occlusion in 2[illegible] per cent of their autopsy material. In a recent study, Ehrlich and Shinohara[illegible] sectioned the entire supplying arterial system of acutely infarcted areas but failed to detect fresh thrombotic occlusion in more than one half of 29 infarcted hearts. Master[illegible] has repeatedly called attention to the occurrence of subendocardial necrotic lesions in the absence of coronary occlusion, and Likoff and associates[illegible] noted electrocardiographic myocardial infarction patterns in patients with normal coronary arteriograms. In 6 out of 25 cases with widespread disseminated and in part grossly visible subendocardial necroses, Horn and associates[illegible] found arterial involvement entirely missing or only minimal.

Myocardial lesions similar to those seen in human coronary heart disease have been produced in animals with perfectly normal coronary vessels in large numbers and by a great variety of experimental procedures (see Section F).

Impairments of the myocardial oxygen supply resulting from anemia, disturbed oxygen delivery by the red cells, shock, pulmonary and coronary embolism, valvular lesions, malformation, and cardiac trauma will not be discussed here since they do not commonly contribute to ordinary "coronary" and degenerative heart disease.

B. Role of ventricular intramural hemodynamics and microcirculation

The crucial feature in the development of the syndrome of "coronary" heart disease is in all likelihood a discrepancy between oxygen supply to and oxygen consumption by the myocardial cells. Even in the presence of an anatomically intact coronary vascular tree, certain areas of the heart muscle, notably the subendocardium of the left ventricle and septum, are at a disadvantage because of a poorer vascular supply[illegible] and because intraventricular pressure and systolic myocardial contraction compress the coronary ramifications and capillaries.[illegible] The exceptional vulnerability of these areas exposes them to the danger of local anoxia whenever myocardial oxygen consumption transcends a certain critical limit. Intravascular cell aggregation in poorly perfused small vessels may constitute an additional locally anoxiating factor.[illegible]

Ordinarily, augmentations of myocardial oxygen consumption are accompanied by

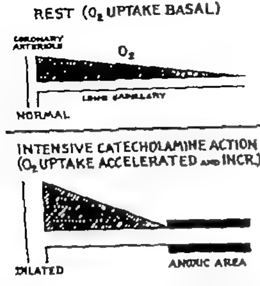


Fig 1 Presumable microcirculatory origin of focal myocardial anoxic necrosis (*black*) at the end of long capillary under influence of intensive cardiotoxic catecholamine action despite full dilatability of coronary system. Shaded areas symbolize decreasing amounts of available oxygen in capillary blood flowing from left to right. Dilated vessels provide more oxygen but length of capillary and rapidity of oxygen uptake create "handicap" for cells at extreme end of capillary

an adequate compensatory dilatation of the coronary system[31-33] Thus, as long as coronary functional dilatability remains intact only extraordinary intensifications of the cardiac oxydative processes may be expected *to cause injurious degrees of* anoxia in cell groups whose oxygen supply is handicapped by extravascular compression and possibly by an unfavorable location at the end of long capillaries[19 20] (Fig 1) The situation becomes quite different, however if coronary dilatability is impaired (see Section E)

C. Role of myocardial oxygen consumption

Despite the fundamental importance of myocardial oxygen expenditures in codetermining the above mentioned pathogenic discrepancy between cardiac oxygen supply and consumption relatively little attention is being paid in everyday clinical reasoning to this decisive factor While no one would attempt to evaluate the financial status of a person or corporation exclusively in terms of income without regard to expenditures such semirational thinking is frequently encountered in statements concerning the pathogenesis of coronary heart disease.

The introduction of the terms coronary insufficiency[7,30 34] and coronary failure[35] was useful because of their greater emphasis on the mutual relativity aspect of myocardial oxygen supply and requirement Thus is also clearly implied in Blumgart's dictum "The changes in the myocardium depend solely on the extent and duration of the relative ischemia not on the manner *in which they are produced*

The reason for the persistence with which the factor of myocardial oxygen consumption is so widely disregarded or belittled seems to rest largely in the pathophysiologic complexity of the problem especially as far as the neurohormonal and hormonal biochemical regulation of the oxydative processes in the heart muscle is concerned Comprehensive reviews of the international literature on this subject have been presented elsewhere[1 30 41] and only some salient points will be enumerated here.

D. Role of sympathetic nerve and catecholamine activity in myocardial oxygen economy

1 Myocardial oxygen consumption is dominated by sympathetic nerve activity via the discharge of the neurogenic catecholamines norepinephrine from the intramyocardial nerve terminals directly into the heart muscle, and epinephrine from the adrenal medulla into the blood (It is important not to confuse the local purely adrenergic effect of norepinephrine physiologically liberated within the heart muscle, and the mixed adrenergic antiadrenergic action elicited by the artificial introduction of norepinephrine into the blood circulation. The latter includes pressoreceptor-mediated vagal stimulation and central sympathetic inhibition)

2. Both catecholamines augment the uptake and consumption of oxygen by the heart muscle far beyond and to some extent independently of the energy requirements of cardiac external mechanical work performance

3 Normally the resulting losses of oxygen are [illegible] compensated fo

by prompt dilatation of the coronary arteries, unless catecholamine action is excessively intense and/or prolonged. In this latter case subendocardial necroses develop in hemodynamically handicapped areas of the heart muscle even in the presence of a normally dilatable coronary system (Fig. 1).

4. If coronary dilatability is reduced (e.g., by experimental partial restriction or by atherosclerosis), augmentation of sympathogenic catecholamine activity is accompanied by severe regional anoxia (Figs. 2 and 3) followed by local necrosis, depending on the degree and duration of the catecholamine induced discrepancy between oxygen supply and consumption.

5. Sympathetic activity is governed by the hypothalamus with participation of the peripheral sympathetic ganglia and nerve endings. It is subject to reflex stimulation by practically all types of stress, including physical exercise, emotional excitement or tension, sensory stimuli, nicotine, trauma, infections, abnormal temperatures, burns, physical restraint, shock, general hypoxia, etc. Under all of these conditions and after direct stimulation of the hypothalamus, an augmentation of catecholamines has been demonstrated in the urine or blood and also in the heart muscle itself. The latter differs from skeletal muscle by its specific avidity to absorb and store both epinephrine and norepinephrine.

6. The thyroid hormone augments the oxygen-wasting properties of the catecholamines and thus aggravates their potential cardiotoxicity. Adrenal mineralocorticoids which are liberated in excess under stressful circumstances together with the catecholamines sensitize the myocardium to the necrotizing action of the latter.[41]

7. The anoxiating cardiotoxic action of the sympathogenic catecholamines reduces the myocardial glycogen stores, phosphocreatine, ATP, and potassium, thus creating alterations in myocardial intermediate metabolism which are identical with those seen in man in advanced degenerative heart disease with infarction and or congestive failure.

8. An exaggerated overactivity of the sympathetic nervous system is normally prevented by counterregulatory sympatho-inhibitory mechanisms, located in the anterior hypothalamus. These are put into action acutely by the vascular pressoreceptors, and in a sustained fashion by habitual

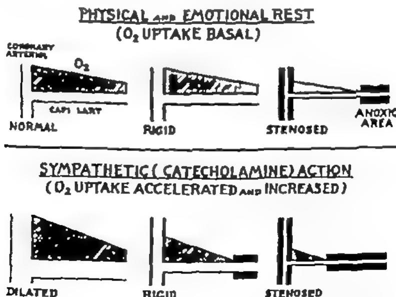


Fig. 2. Microcirculatory origin of focal myocardial anoxic necrosis (*black*) due to decrease in available oxygen (*shaded*) which is caused by an increasing discrepancy between oxygen consumption (augmented by cathecholamine action) and compensatory coronary dilatability (impaired by sclerosis and/or compression of arterioles).

physical exercise. By contrast, lack of exercise causes a deficiency of antiadrenergic counterregulation and thereby elicits a chronic adrenergic preponderance in the heart muscle (The vagal cholinergic system reduces the heart rate via the atrial nodes but has no neuron representation in the ventricles and probably does not exert any significant direct influence on ventricular function and metabolism.)

E. Experimental catecholamine-induced myocardial lesions without or with coronary impairment

The experimental production of disseminated focal necroses in the subendocardial layers of the left ventricle by injections of epinephrine or of norepinephrine has been observed by many investigators since 1907.[1, 9] Subthreshold cardiotoxicity due to small doses per time unit becomes manifest if they are infused over hours or days.[9] Likewise prolonged electrical stimulation of the norepinephrine-discharging cardiac sympathetic nerves,[49, 201] and experimental lesions or stimulations of the brain stem[7 ... 29] have been found to elicit electrocardiographic signs of hypoxic myocardial damage and subendocardial hemorrhages and necroses.

Infarction-type electrocardiograms[3] and disseminated necrotic foci and infarctions were observed in vascularly normal hearts of baboons which had been subjected to sustained or acute emotional stresses.[13, 21]

Similar foci of destruction usually of microscopic size, appear regularly in the ventricular myocardium of corticoid-sensitized rats after application of a variety of physical stresses (restraint, exposure to cold and heat, forced exercise, surgical trauma, etc.[9, 31]) and after exogenous administration of catecholamines[9, 13, 34] or of cathecholamine liberating nicotine.[36] The stress-induced myocardial necroses can be prevented by antiadrenergic drugs,[10] hypothalamic inhibition[37, 38] and section of the reflex pathways in the cervical cord.[37] Epinephrine-induced myocardial necrosis formation is greatly aggravated by thyroxin.[9]

During experimental restriction of major coronary branches, the injection of catecholamines, direct or reflex stimulation of the cardiac sympathetic nerves (muscular exercise)[39] and injection of nicotine[39] are accompanied by the electrocardiographic signs of severe myocardial anoxia (marked elevation of S-T) (Fig 4)

Pre-existing anatomic lesions of the coronary arteries, produced in rats by an overdosage of parathyroid hormone[1] or in rabbits and dogs by cholesterol feeding markedly enhance the myocardial destructive effects of injected catecholamines[2, 4] or of catecholamine-liberating stresses.[29, 4]

It may be assumed that a reduction in compensatory dilatability of the sclerotic coronary vessels[12, 20] in conjunction with stress (=catecholamine)-induced myocardial oxygen wastage, subendocardial vasocompression and shortening of the ventricular diastole is responsible for these detrimental effects.

It also seems significant that stimulation of the cardiac sympathetic nerves has been found to increase the rapidity of development, the size and the fatal outcome of myocardial infarctions elicited by coronary ligature,[64] whereas bilateral thoracic sympathectomy or infiltration of procaine into the left stellate ganglion exerted an opposite protective effect.[65]

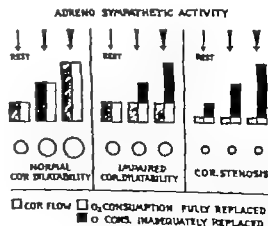


Fig 3 With decreasing compensatory coronary dilatability (*circles*) and increasing sympathetic activity (*arrows*), the discrepancy (*black*) between coronary oxygen supply on the one hand (*shaded areas on left*), and neurogenic, catecholamine-induced additional myocardial oxygen consumption on the other (*total areas on right*) will increase thus leading to anoxia in the vascularly "handicapped" cell groups of the heart muscle. (From Raab, Revue Canadienne de Biologie 22:217 1963 by permission.)

F. Role of cardiac work and of sympathogenic catecholamines in the clinical syndromes of coronary heart disease[16]

The [illegible] of the clinical manifestations of coronary heart disease such as the [illegible] occurrence of anginal [illegible] rhythmias, fluctuations [illegible] abnormalities and [illegible] of congestive failure [illegible] the assumption of a state [illegible] that [illegible] causal mech[illegible]

There [illegible] taken for granted [illegible] implied that augmenta[illegible] work [illegible] count for whatever [illegible] oxygen want may be [illegible] without clinical [illegible] and beyond those which [illegible] coronary insufficien[illegible] and emotional rest. Th[illegible] universally adopted concept [illegible] increases in cardiac work during physical exercise or emotional [illegible] associated both with augmented cardiac oxygen expenditure and with a hypothalamus-triggered [illegible] discharge of catecholamines. The influence of the catecholamines on myocardial oxygen consumption [illegible] transcends the metabolic requirement of the amount of work actually performed by the heart.[31,90,32] This oxygen wasting effect of sympathetic catecholamine [illegible] is [illegible] and so independent of myocardial external work performance per se that it could be demonstrated even during artificial reduction of the latter.

In animal experiments with partial coronary restriction the electrocardiographic signs of severe myocardial anoxia could be provoked by sympathetic stimulation which caused only minimal augmentations of cardiac work, whereas the imposition of heavy noncatecholamine induced work loads on the heart (electrical sinus tachycardia, angiotensin II hypertension) failed to produce this effect. Patients with coronary sclerosis are prone to display electrocardiographic indications of myocardial hypoxia and to experience anginal pain coincident with the catecholamine discharges physiologically provoked by exercise (see above) and emotions.[41,95]

A causal relationship between increased cardiac work as such and the origin of anginal symptoms has never been clearly established. On the contrary, careful clinical observations have revealed a far reaching mutual independence and disproportionality between the magnitude of cardiac work on the one hand and the simultaneous occurrence of anginal symptoms on the other.[36] It seems to be hardly justified, therefore, to attribute the electrocardiographic signs and the symptoms of myocardial hypoxia connected with physical exercise[19,75] or with emotional excitement[67] primarily to the associated augmentations of cardiac work. Rather they appear to be caused by the specifically "myocardial oxygen wasting" biochemical action of the catecholamines whose discharge from the sympathetic nerve terminals within the heart muscle and from the adrenal medulla into the blood regularly accompanies both physical exertion and emotional or other stresses (see Section D).

It may be significant that in some patients with angina pectoris the elevation of the levels of catecholamines in the blood after exercise[4] [illegible][71] and emotional excitement[96] has been found to be abnormally exaggerated and that the hemodynamic functional pattern of such patients suggests a high sympathetic tone.[1] Similar observations were made in cases of congestive heart failure in connection with exercise and the urinary excretion of epinephrine and norepinephrine was found to be markedly increased in advanced cardiac failure.[22] The sensitivity of patients with congestive heart failure to the stress of environmental heat and atmospheric humidity,[96] which augments the cardiac output and stroke volume[96,98] via reflex mechanisms of the central nervous system,[96] may also be tentatively attributed to intensified sympathogenic catecholamine action. According to recent findings[98,99] the failing human heart seems to be using an excessive amount of oxygen in combination with a low degree of energetic efficiency.[96] This in turn is presumably due in part to an interference of myocardial oxygen want in the local formation and utilization of high energy phosphates[10,30] in myocardial

protein metabolism [33] and in the electrolyte balance[34] of the heart muscle.

Augmentation of lactic acid as well as of excess lactate [44] in the coronary sinus blood is a characteristic anoxia-revealing effect both of injected epinephrine in animals[45] and of exercise or injection of isoproterenol in patients with coronary sclerosis.[4]

The profound influence of sympathetic catecholamines in causing a critical exhaustion of a subnormal coronary reserve,[7-9] and their corresponding pathogenic role are now increasingly recognized also by clinical investigators.

II Factors which exaggerate potentially pathogenic cardiac sympathetic activity

Animal experimentation has provided abundant direct evidence of the potentially myocardium injuring action of extrinsic as well as intrinsic sympathogenic catecholamines (see Section E). By contrast the pathogenic significance of clinical sympathetic and adrenal medullary over activity in contributing to structural damage of the human heart can be concluded from indirect evidence only.

Typical hypoxic changes of the electrocardiogram are frequently seen in patients with pheochromocytoma during paroxysms, but neither coronary sclerosis nor degenerative lesions of the myocardium have been reported with regularity, possibly because of the relatively young age of autoptically verified cases, and because of the mounting resistance against cardiotoxic effects which results from repeated catecholamine stresses of a certain intensity.

On the other hand subendocardial necroses *and infarctions without coronary* occlusion have been observed in connection with tachycardia and with such stressful events and conditions as acute heart failure, pulmonary embolism, dissecting aneurysm of the aorta, postoperative shock, and severe infections,[21-23] all of which are known or may be assumed to be associated with a massive influx of catecholamines into the heart muscle (see Section D5) and with augmented adrenal cortical activity (see Section H).

The stress of acute physical exertion with its accompanying catecholamine discharges *remains innocuous as long as the* coronary system is fully dilatable. However, in the presence of coronary restriction[44] or experimental[19] or clinical coronary sclerosis it is prone to elicit the functional and structural sequelae of myocardium anoxiating coronary insufficiency.

There is only little reason to suspect a causal connection between acute stimulations of the sympathoadrenal system and the sudden development of occluding coronary thrombosis. However, the studies of Paterson suggest the possibility that stress-induced and pressure-induced coronary intra intimal capillary ruptures and hemorrhages in coronary *arterial* walls may contribute to a slowly develop-

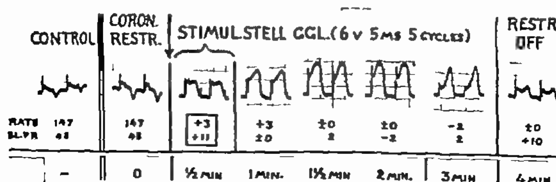


Fig. 4 Stimulation of the cardiac sympathetic nerves (stellate ganglia) of the cat during one-half minute causes severe myocardial anoxia for several minutes if compensatory coronary dilatation is prevented by restricting (not occluding) ligature of the regional coronary branch. (From Raab et al. American Journal of Cardiology 9:353, 1962, by permission.)

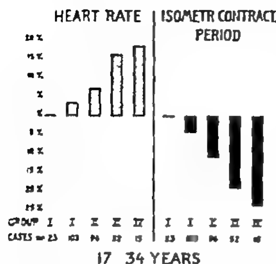


Fig. 5. Increase in resting heart rate and shortening of isometric contraction period of left ventricle (criteria of chronotropic and inotropic sympathetic preponderance) in proportion to decreasing exercise habits in groups of 289 healthy men, ranging from ... athletes (Group I+) to completely sedentary individuals (Group III) indicative of ... sympathoinhibitory ... The same pattern ... found in older age group (35-40 years). (From Raab et al.: American Journal of Cardiology 5:300, 1960. By permission.)

ing delayed occlusion of the coronary lumen without a clearly discernible time relation to the provoking stress.

Of greater general pathogenic and epidemiological significance than acute episodes of severe sympathoadrenal overactivity seem to be the sustained elevations of the basal cardiac sympathetic tone and the superimposed moderate but incessant catecholamine aggressions to which our overcivilized way of life exposes the myocardium. In the presence of dilatability-impairing coronary arteriosclerosis by which increasingly young age categories of people in the Western nations are affected,[228-230] even slight but prolonged augmentations of sympathetic catecholamine activity may be expected to contribute to insidiously progressing subclinical derangements of myocardial oxygen economy ultimately resulting in overt destruction of tissue and functional failure of the heart muscle. Extended emotional and environmental stresses, tobacco smoking, and lack of physical exercise are identifiable main factors in the causation of civilization induced cardiac neurovegetative disequilibrium.

1. Emotional stress. A high incidence of "coronary heart disease" has been observed in mentally overtaxed, emotionally tense, high-strung and competitively striving individuals.[1, 231-234] An augmented excretion of catecholamines[235] and of the catecholamine metabolite vanillin mandelic acid (VMA)[236] in the urine and an elevation of catecholamine levels in the plasma[237] can be considered to be a specific indication of increased sympathetic activity in these groups of people and under emotional stress in general. Recent observations of our own revealed a high cardiac sympathetic tone at rest and an accentuated cardiac reactivity to a standard mental stress in emotionally excitable individuals.[238] (Exaggerated reactive elevations of the level of catecholamines in the blood of patients with angina and of those with congestive heart failure have been mentioned in Section F.) In this connection it is of interest that Somali herdsmen who lead an unusually emotionally placid life were found to be free from heart disease despite the fact that their nourishment consists almost entirely of camel's milk (about 5 liters daily).[239]

The apparent occurrence of nonocclusive disseminated myocardial injuries with delayed clinical consequences[17] as a result of acute emotional catecholamine bombardments of the heart muscle is bound to raise delicate insurance problems,[224] different from those which are concerned with clear cut occlusion-induced transmural infarctions.

2. Sensory stimuli and stresses. Sensory stimuli and stresses, such as industrial and traffic noises, flickering light, etc., have been found to provoke sympathogenic cardiac reactions (acceleration, increase of cardiac output[240, 241] and of stroke volume[242]) and to be accompanied by an increased urinary excretion of epinephrine and norepinephrine.[243] (In rats similar sensory stimuli caused metabolic alterations in the heart muscle analogous to those elicited by catecholamine action.[244])

3. Nicotine. The sympathetic-stimulating effects of nicotine and tobacco smoking and the corresponding adrenergic cardiac reactions have long been known. They

are accompanied by an augmentation of catecholamines in the blood[81] urine[127] and heart muscle[41] and by an increase in myocardial oxygen consumption[32] In the presence of coronary restriction nicotine elicits the electrocardiographic signs of myocardial anoxia.[38]

A significant role of tobacco smoking in the incidence of coronary heart disease is suggested by extensive statistical studies.[131, 134-141]

4 Habitual physical inactivity Habitual physical inactivity is associated with a progressing deficiency[142, 43] of the sympathoinhibitory[224, 228] and vagal mechanisms which normally keep cardiac sympathetic chronotropic and inotropic activities within certain limits at rest as well as during exercise[142, 4] The characteristics of the sympathicotonic loafer's heart[47] (relatively high rate short isometric contraction period proneness to develop hypoxic ECG changes during exercise low efficiency) are the diametrical opposite of those of the well trained athlete's heart with its low sympathetic tone and high efficiency[4] (Fig 5)

Civilization-induced behavior patterns ("fight and flight" emotions without commensurate muscular action[143, 242]) have been made responsible for the purposeless disproportionate cardiac sympathetic overactivity of Western man[244, 245] which is comparable to racing the engine of a nonmoving automobile

According to recent studies, the cardiac sympathetic tone seems to be influenced by metabolic processes in the skeletal musculature.[246]

A causal link between lack of physical exercise and the incidence of coronary heart disease" with myocardial degeneration and infarction seems well established by a steadily growing number of statistical studies[147] among which those of Morris[148] Brunner[4] and Myasnikov[66] are particularly noteworthy The data of Morris and Crawford[148] strongly suggest that lack of exercise is not so much responsible for coronary vascular damage as for primary myocardial vulnerability

A possible prognostic significance of an elevated heart rate (generally a criterion of either an absolute increase in sympathetic activity or of inadequate sympatho-inhibition) has been suspected by Luongo[11] and Paul and associates.[126]

II Subsidiary hormonal factors

1 Adrenal corticoids The well known augmentation of adrenal cortical secretory activity under a variety of stresses,[7] including nicotine[48] may conceivably constitute an important subsidiary pathogenic element by aggravating catecholamine-induced neurogenic myocardial lesions. This assumption appears to be justified in view of the fact that the experimental production of severe myocardial necroses through various catecholamine-liberating stresses and through injection of catecholamines is greatly facilitated by the preceding and accompanying administration of corticoids.[9, 21, 51] By contrast the antimineralocorticoid agent spironolactone exerts a protective effect[51]

Significant increases in cortical steroids in blood and urine have been observed in animals and in human beings under emotional[132, 133, 134] and acoustical stresses[133, 135] whereas emotionally soothing situations (watching nature study films) produced an opposite effect[137]

2 Thyroid hormone. Interference of the thyroid hormone in the pathogenesis of coronary heart disease is ambiguous in that it prevents coronary atherogenesis, on the one hand while potentiating the oxygen-wasting, myocardial-hypoxiating effect of the catecholamines, on the other[144, 138] Thus, its indirect cardiotoxicity is greatly mitigated by its simultaneous protective influence on the structure of the coronary arteries.[144] Once coronary sclerosis is established however thyroid activity can contribute significantly to provocation of the anginal syndrome as well as of congestive heart failure.[137, 139]

3 Pitressin Pitressin the only known biological agent with definite coronary constricting properties, is believed by Russian investigators to be slowly and belatedly liberated into the blood stream after intensive hypothalamic and sympathetic stimulations. This concept might help to explain the occasionally delayed occurrence of anginal symptoms within hours after a stressful event

4 Estrogens Although an antiatherogenic influence of the estrogens is well

established it is still a moot question whether their effectiveness in preventing recurrences of myocardial infarctions[4, 61] might be due in part also to a favorable action on myocardial metabolism.

5. *Insulin.* Attacks of angina pectoris which occur during states of spontaneous hypoglycemia[61, 62] or after an overdosage of insulin[63] are probably to be attributed essentially to the accompanying reactive discharge[1] and resulting myocardial accumulation[64] of catecholamines.

6. *Parathyroid hormone.* The parathyroid hormone favors the deposition of calcium both in the coronary wall and in the myocardium.[1] Extensive calcifying cardiac necroses have been produced by experimental overdosage of parathyroid hormone in conjunction with adrenal corticoids and renal excretory failure[65, 6] and are occasionally seen in clinical hyperparathyroidism.[66]

I. Role of blood pressure, cardiac hypertrophy, renal failure and thiamine deficiency

Acute falls in the systolic blood pressure as in hemorrhagic, post-traumatic or infectious shock,[71, 89] or after the administration of antihypertensive drugs[1, 7] can produce transient myocardial hypoxia with or without resulting structural damage by diminishing coronary flow and oxygen supply and may in addition favor the development of thromboses in the coronary system.

Such sporadic episodes are, however, of only minor pathogenic importance compared with that of *sustained arterial hypertension.* In the Framingham study[171] and other studies,[174] hypertension was found to precede and accompany the development of overt coronary heart disease as a highly significant contributory factor.

The fact that the *diastolic pressure* tends to fall during physical exercise due to vasodilatation in the skeletal muscles, whereas it remains unchanged or rises during emotional stress, may account for the clinical experience that the sympathetic stimulation which accompanies physical exertion is sometimes better tolerated by persons with coronary sclerosis than is that associated with emotional excitement.

Cardiac hypertrophy accentuates the risk of coronary heart disease even further than arterial hypertension per se.[172] Both of these conditions seem to increase the vulnerability of a poorly vascularized heart muscle. Hypertension, by raising the intraventricular pressure, causes an intensified compression of subendocardial coronary ramifications, while at the same time augmenting ventricular oxygen demands. Left ventricular hypertrophy augments the oxygen requirements of the individual myocardial cell while presumably curtailing the availability of oxygen to the enlarged cell body.[173, 7]

Acute congestive heart failure has been cited as a contributory factor in the development of subendocardial necroses,[21] but in such instances a distinction between cause and effect cannot be clearly drawn.

The reduced urinary excretion[23, 167] and the accumulation of catecholamines in the blood[175] of patients with advanced *renal excretory failure* may serve as a myocardial vulnerability augmenting factor, at least in the presence of pre-existing cardiac damage.[175] Necrotic lesions of the myocardium are common in uremia,[1] conceivably also because of increased adrenal corticoid and parathyroid hormone action.[65, 6]

Thiamine deficiency is associated with an accumulation of catecholamines in the heart muscle of experimental animals.[1, 4, 177] Clinical hemodynamic and electrocardiographic manifestations of the adrenergic type, ending in congestive failure and necrotic lesions of the myocardium, which are frequently seen in thiamine deficiency,[1] may be explained on this basis.[178]

J. Role of electrolytes

Investigation of the role of myocardial electrolyte metabolism in the origin of functional and structural cardiac pathology is in a state of flux.

Dietary potassium deficiency and other losses of body potassium are known to elicit focal necrotic lesions of the heart muscle.[179-181] On the other hand, anoxia of myocardial tissue is followed by a rapid local depletion of potassium from the affected areas.[82, 1]

There is some evidence that administered catecholamines[11, 31, 184] and catecholamine-liberating stresses[43] cause an extru

tion of potassium from the heart, i.e., presumably only from anoxia-injured cell groups. This fact and the electrocardiographic similarities of catecholamine action, myocardial anoxia, and potassium depletion on the one hand [78] and of coronary heart disease on the other point again toward common causal relationships. The island-like distribution of electrocardiographic S-T displacements over the surface of the ventricles in cases of angina pectoris [19] may be related to the dissemination pattern of potassium-depleted foci of anoxia in the myocardium (see Sections B and D).

From the clinical point of view, the most significant aspect of Selye's experiments with the administration of unphysiologically massive myocardium-necrotizing doses of sodium salts is the effective prevention of these severe necroses by potassium.[8,27] Sodi Pallares [81] has succeeded in normalizing the electrocardiograms of patients with fresh myocardial infarction or chronic myocardial ischemia by means of a "polarizing" treatment with potassium in combination with glucose and insulin.

K. Role of fats and lipids

Since this review is not concerned with problems of coronary atherogenesis and thrombus formation, only the question of a possible involvement of fats and lipids in the primarily myocardial vulnerability features of "coronary heart disease" will be considered here.

Fatty acids and triglycerides are normally extracted from the blood and oxidized by the heart muscle.[88,189] It is also known that sympathetic stimulation and catecholamines liberate free fatty acids from adipose tissue.[187] Accordingly, emotional excitement, anger, anxiety, [88] and cigarette smoking[137] were found to be associated with an increase both in urinary catecholamines and in serum free fatty acids. Both of these reactions disappear during ganglionic blockade.[137]

In patients with myocardial infarction the response of the serum free fatty acids to cigarette smoking was found to be augmented.[194] The development of corticoid-induced plus electrolyte-induced myocardial necroses was intensified after the feeding of various fats [42] and rabbits which were fed fat plus cholesterol displayed an accentuated sensitivity of the heart to norepinephrine.[291] Infusion of norepinephrine increased the triglyceride content of the heart muscle.[290] Statements in regard to the response of the blood fatty acids and cholesterol to acute or prolonged physical exercise are contradictory.[11,143,244]

Serum cholesterol and triglycerides usually rise in connection with emotional stress.[248,294] However, it appears doubtful that, apart from their importance for atherogenesis, fats and lipids play more than a passive role in myocardial metabolic derangements and structural degeneration.

L. Therapeutic aspects

Methods designed to restore and maintain an adequate coronary blood flow by surgical revascularization, coronary dilatation, and anticoagulation do not fall within the scope of the present review.

Since the occurrence and the degree of anoxic myocardial lesions and of their sequelae are determined by the magnitude of the discrepancy between coronary oxygen supply and myocardial oxygen consumption, various therapeutic procedures are being used to reduce the latter, especially in the presence of coronary sclerosis and fixed coronary flow. Some of these therapeutic devices can be assumed to act by diminishing the production and reflex discharge of the oxygen-wasting catecholamines: physical rest, avoidance of emotional excitation, hypothalamic depressants, thoracic sympathectomy, ganglionic blockade, x-ray irradiation of the adrenals and thoracic sympathetic chain areas, monoamine oxidase inhibitors (whose therapeutic effect is attributed to an inhibition of intramyocardial catecholamine release), and digital compression of the carotid sinus which stimulates sympatho-inhibitory mechanisms in the central nervous system (to stop attacks of angina pectoris and pulmonary edema). Inactivation of cardiac oxygen-consuming catecholamine action is achieved by thyrostatic interferences (thyroidectomy, thiourea drugs, radioiodine). Myocardial catecholamine-depleting drugs (reserpine, guanethidine) are less useful than one might expect, probably because their catechol

[illegible]ine-depleting effect is paralleled by an augmentation of myocardial sensitivity [illegible] techolamine. The administration of th[illegible] ine removes excess accumulations [illegible] techolamines from the myocardium [illegible] experimental [illegible] amine deficiency and [illegible] in th[illegible] e ert[illegible] beneficial a tion [illegible] on the metabolically injured beriberi heart. More detailed reviews of anti[illegible]drenergic therapeutic techniques are presented elsewhere.[illegible]

Recently [illegible] attempts have been made [illegible] correct the [illegible]-induced losses [illegible] myocardial potassium in coronary heart disease by administering potassium together with glucose and insulin[illegible] or in the form [illegible] potassium aspartate which [illegible] supposed [illegible] facilitate the deposition of th[illegible] tion in the heart muscle.[illegible]

The observation [illegible] of Mel[illegible] and Korol [illegible] that [illegible] retain potassium [illegible] heart assumes added interest [illegible] of newer findings in regard to [illegible] coronary dilator [illegible] coronary blood flow in the presence [illegible] advanced clinical coronary sclerosis[illegible] and in connection with [illegible] experimental observation concerning the suppression of epinephrine-induced electrocardiographic changes by nitroglycerin.[illegible]

Magnesium which exerts heart protecting effects similar to those of potassium[illegible] has been reported to be therapeutically effective if applied by transthoracic iontophoresis[illegible] or as magnesium aspartate.[illegible]

Antihypertensive and shock preventing forms of therapy contribute to the protection of the myocardium from detrimental hemodynamic extramural and intramural disturbances of coronary blood supply (see Section B).

M. Preventive aspects

The most encouraging prophylactic aspect of the often crucially decisive neurovegetative adrenergic factor in myocardial vulnerability to existing coronary vascular disease is the potential reversibility of this factor in the early premorbid stage and even in the presence of moderately advanced heart disease.

Established anatomic coronary vascular lesions are generally permanent and irreparable. By contrast, the environmental emotional and nicotine-induced overstimulation of the cardiac sympathetic system and the physical inactivity induced deficiency of sympathoinhibitory counterregulation[illegible] (see Section G) can be prevented or corrected by a change of environment, deliberate emotional relaxation, abstinence from smoking, and systematic physical training[illegible] (Fig. 6).

These principles, combined with a thorough indoctrination in health rules, such as indefinitely continued exercises at home, hiking, sports, cold showers, creative utilization of leisure time, fat-poor diet, etc., constitute the rational foundation of the preventive health programs which are practiced in nearly three thousand government, industry, and insurance-sponsored scenic rural reconditioning centers in Europe.[illegible] Preliminary studies in regard to the immediate and long-range cardiac neurovegetative effects of these mass reconditioning systems in sympathicotonic individuals have uniformly revealed a prolonged shift toward improved sympathoinhibitory counterregulation (reduced heart rate, prolonged isometric contraction period, lowered blood pressure). Detailed data on these observations have been reported elsewhere.[illegible] Recent observations of our own suggest an effective reduction of emotionally induced overexcitability of the cardiac sympathetic system by habitual physical exercising.[illegible]

In connection with the emphasis placed at the European reconditioning centers on physical training and cold water applications, it appears significant that, on the basis of extensive series of stress-resistance developing experiments in animals, Selye arrived at the conclusion that "pre-treatment with cold baths or muscular exercise is the most generally cardio-protective agent so far revealed by animal experimentation."[illegible]

About five million people are being sent annually to thousands of reconditioning centers abroad. It seems paradoxical, indeed, that in the United States of America, where mortality from coronary heart disease [illegible] unsurpassed, no attention is being paid by the government and by private agencies to the large-scale preventive cardiac reconditioning system which [illegible]

been applied in other much less afflicted countries for many years with apparent success.[11, 111] Scientifically supervised physical training programs in urban areas are being conducted for "coronary prone" and elderly pre-patients by Dr K. H. Hellerstein, Dr T. K. Cureton and Dr B. Balke in Cleveland, Urbana, Illinois, and Oklahoma City, respectively.

Our record of nearly 250,000 premature cardiac deaths (in persons under 65 years of age) per year with an annual loss of 4.2 billion dollars from heart disease to the nation's economy[222] makes it imperative that the responsible authorities direct their initiative in planning and acting toward all investigative and practical aspects of the problem which justify a reasonable hope for the control of this country's permanent national cardiac health emergency.

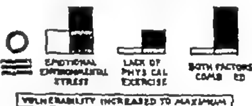
N. Investigative aspects

One reason for the reluctance of the American medical profession and health authorities to adopt the measures taken by other nations in these matters seems to be a disproportionately unilateral preoccupation with the problems of vascular atherogenesis at the expense of interest in the primarily myocardial metabolic and neurovegetative aspects of coronary heart disease. By contrast, A. L. Myasnikov, the leading cardiologist of the Soviet Union, who distinguishes explicitly between "coronarogenic" and "noncoronarogenic" (metabolic and neurogenic) myocardial necroses, urges a revision of the traditional mechanistic concepts of myocardial necrosis and infarction in the light of modern information on primarily chemical and neurohormonal (catecholamine) influences on the heart muscle.[114]

I can hardly be suspected of bias against the dietary features of prevention. As a result of my own early world-wide epidemiological inquiry,[12] I have for the last 24 years pleaded for preventive dietary measures (reduction in the intake of dairy products, meat fats, and total calories, emphasis on cereals, vegetables, fruit and fish[117]). These recommendations were almost identical with those finally adopted by the American Heart Association[11] and American Medical Association[21] in 1961 on vastly consolidated evidence.

Nevertheless, I feel that much of the effort and resources which are now being devoted to repetitious confirmations of results which had been obtained from previous extensive studies could be more profitably diverted toward a systematic concentration on the so far only sporadically explored field of primarily metabolic and neurogenic hormonal "myocardial vulnerability." Recognition of its fundamental pathogenic significance as well as of the possibilities for practical active prevention which it offers holds great promise for the academic investigator, the public health organizer, and last but not least





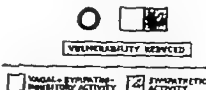


Fig 6 Neurovegetative disequilibrium (potentially hypoxiating sympathetic preponderance, black) threatens myocardial metabolic and structural integrity if coronary compensatory dilatability is impaired (cf Fig 2). The underlying mechanisms—(a) hypothalamic-sympathetic stimulation by stresses (including nicotine), and (b) deficiency of vagal + sympathoinhibitory counterregulation resulting from lack of exercise ("loafer heart")—are reversible. Appropriate neurovegetative reconditioning procedures promise preventive reduction of myocardial vulnerability to irreversible coronary sclerosis.

for all our gravely endangered overcivilized, underexercised, and emotionally harassed contemporaries.

Coronary heart disease may be considered to be the result of an integrated although fluctuating pathogenic triad: (1) atherogenic diet, (2) environmental, emotional, and nicotine-induced overstimulation of the sympathoadrenal system, and (3) deterioration of cardiac sympathoinhibitory counterregulation due to physical inactivity. Investigative projects concerning pathogenesis and prevention which disregard the two latter factors cannot be expected to yield conclusive results. This was implied in recommendations recently made by the World Health Organization[88] and by the American Heart Association.

One of the first logical steps toward a suitable investigative program would be the establishment of a pilot experimental reconditioning center in an appropriate scenic and climatic location for the objective study of the effects of environmental and emotional relaxation plus outdoor physical training on the cardiac neuroregulative equilibrium. Sedentary cardiologists, physiologists, practicing physicians, public health officers, and other intellectually qualified prospective victims of coronary heart disease would constitute an ideal test subject material both for critical self-observation and for systematic objective study. Admission to such a center would carry the obligation that the test subjects continue reconditioning procedures indefinitely and keep themselves available for long-range follow-ups including retesting.

Above all sophisticated theoretical considerations, however, hovers the supremely urgent question posed by G. C. Griffith[89]* at the Fourth World Congress of Cardiology in Mexico City in 1962: Can the profession wait 5 to 10 years for such a study, neglect the facts, and wait for final proof or should we institute intelligent control measures for the prevention of coronary heart disease now? (*See note, p. 699.)

Summary

Common use of the cliché "coronary heart disease" has created a disproportionately one-sided preoccupation with the vascular anatomic aspects of degenerative heart disease to the detriment of interest in those metabolic and neuroregulatory factors which determine the degree of myocardial vulnerability.

Myocardial oxygen economy and health depend equally on vascular oxygen supply and myocardial oxygen consumption. The latter is dominated by sympathetic neurohormonal (catecholamine) activity.

Myocardial cell vulnerability in the presence of an impaired compensatory dilatability of the coronary arteries (coronary sclerosis) is maximal in certain hemodynamically handicapped areas of the left ventricle. It is augmented by sympathogenic catecholamine action through (a) an increase in cardiac oxygen consumption, (b) shortening of diastolic coronary flow, (c) systolic compression of coronary ramifications, especially in the subendocardial layers, (d) presumable losses of potassium from anoxic myocardial cells. Adrenal corticoids and the thyroid hormone intensify catecholamine-induced myocardial vulnerability.

The oxygen requirements of cardiac external work per se seem to be less responsible for the occurrence of myocardial anoxia than are the specifically oxygen-wasting and unfavorable microcirculatory effects of associated catecholamine liberation, e.g., during emotional excitement, exercise, and other stresses.

Most of the procedures and agents designed for the treatment of the clinical manifestations of ischemic heart disease act by decreasing adrenergic metabolic myocardial vulnerability.

Civilization-connected augmentation of primary myocardial vulnerability seems to be caused by emotional and environmental plus nicotine-mediated stimulations of the catecholamine-liberating sympatho-adrenal system, combined with a physical-inactivity induced deterioration of sympathoinhibitory and vagal counterregulation.

These pathogenic neurovegetative mechanisms are reversible and, therefore, of outstanding importance from the point of view of active prevention. Mass preventive cardiac reconditioning systems, aimed at restoring the myocardial neuroregulatory equilibrium of fatigued, tense, and sedentary individuals, are organized abroad on

a large scale by governments and private corporations. No such programs exist yet in the United States.

* "Preventive Heart Reconditioning Foundation" was recently organized in Vermont, with the aim of establishing first, scientifically conducted pilot Heart Reconditioning Center in the Green Mountains. Honorary President: Dr Paul D. White. President: Dr. W. Raab. Directors: Dr G. C. Griffith, Dr. Hans Kraus, Dr D. J. Lauer, Dr E. H. Page, Dr E. W. Seward, Dr H. Selye, Dr J. Stamler and others.

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Fundamentals of clinical cardiology

Viral myocarditis

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During the last two decades, interest in the infectious aspects of heart disease has largely centered on the sequelae of rheumatic fever and various facets of bacterial endocarditis. The problem of cardiovascular syphilis, although still present from the pre-penicillin era, has become less urgent with the advent of appropriate antibiotics.

Recently there has been a revival of interest in a wide variety of infectious diseases which may involve the heart and initiate an inflammatory process. This type of myocarditis is gaining acceptance as a frequent concomitant of the acute disseminated infectious illness. Usually the expressions of this process are subclinical, or subtle and easily overlooked.

Despite the heart's unique although poorly understood mechanisms of resistance it may on occasion be profoundly involved with overt clinical manifestations. In some instances, an evolving process continues and a chronic phase of myocardial disease emerges.

Almost every infectious agent has been implicated as a cause of this disorder including viruses, bacteria, fungi, Rickettsia, spirochetes, and parasites.[1-3] The Mycoplasma, recently uncovered as the major etiological agent in primary atypical pneumonia, has been implicated in some instances by association. Its role in acute respiratory illness, and the recent demonstration that it causes chronic disease in man makes this group of organisms worthy of further investigation.

The virus has received special attention as a potential pathogen and recent reports have suggested the association of myocarditis with infectious mononucleosis,[7] psittacosis, rabies, varicella,[1,4] lymphocytic choriomeningitis,[12] influenza A,[13-17] and the enteroviruses.[4-10] It is likely that reports of this kind will multiply and that new offending agents will be specifically identified as more complete virologic studies are undertaken. Of special importance in this regard is the possible role of virus as an inciting antecedent in many instances of unexplained chronic myocardial disease.

The pathogenesis of acute myocarditis varies with the offending organism. Pyogenic bacteria, such as the staphylococcus, may invade the myocardium directly, forming metastatic abscesses and initiating an inflammatory reaction.[21] Others may elaborate potent toxins which directly lyse myocardial cells or induce thrombotic hemorrhagic lesions of the Schwartzman phenomena.[22,23] The Rickettsia may induce a vasculitis characterized by endothelial proliferation and plugging of small arterioles.[24] The net effect of the virus within the myocardium is poorly understood. There appears to be at least two mechanisms by which the organism may injure

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the heart and ignite a deleterious process. It may damage the heart directly either by the destruction of cells or through an alteration in cellular function, i.e., by affecting essential energy systems or by participating in an antigen antibody complex which gives rise to an autoimmune disease.

It is well known that many viruses exert a dual effect upon the host.[illegible] The direct toxic effect occurs early with multiplication of the virus within the cell. During the indirect or postinfectious phase, no virus can be isolated from the cell and clinical symptoms, if they occur, become apparent to 10 days later. Microscopically the lesions which appear during this "delayed" stage of a viral illness appear to be allergic rather than infectious. The mechanism of hypersensitivity is further corroborated by the normal evolution of these lesions and the development of specific immunity in the agammaglobulinemic patient. These characteristics strongly suggest analogy to a true autoimmune phenomenon.

There is valid empirical evidence to support a direct link between the viral illness and the subsequent development of heart disease. These pieces of incriminating data include (1) the association of a viral illness with a rise in specific antibody titer and the frequent clinical and electrocardiographic evidence of myocardial involvement, (2) the presence of a fatal respiratory infection and acute exudative changes within the heart, (3) the isolation of the virus directly from the heart of infants[illegible] and adults dying with myocarditis,[17] (4) the frequent occurrence of myocarditis during epidemics of influenza,[44] and (5) the production of disease in the experimental animal after the innoculation of live virus.[illegible]

Acute inflammatory myocarditis has been produced with various organisms in a number of animal model systems. It is well known that the production of myocarditis in suckling mice by the Coxsackie B virus is a distinguishing feature of this agent and is a standard criterion used to separate it from other members of the Coxsackie family. Helwig and Schmidt[3] used a virus isolated from a chimpanzee dying of interstitial myocarditis and transferred the disease to mice, hampsters and guinea pigs. In each instance the pathologic changes were strikingly similar to those of the human form of the disease. Pearce[33] utilized successfully six different strains of virus to produce experimental myocarditis and noted that the degree of inflammatory response correlated well with the inherent virulence of the offending organism.

Recently in this hospital a complete virology profile was run on paired sera, nose and rectal swabs and on biopsy material from the hearts of 12 patients with chronic myocardial disease in an effort to isolate an etiological agent. No organisms were recovered, but their absence is not surprising at this stage of the disease. This type of investigation is more apt to yield positive results when a diligent search is extended to the acute and subacute phases of appropriate infections.

The clinical features of viral myocarditis are variable. Subtle electrocardiographic alterations or the development of extrasystoles may be the only suggestion that the heart is involved. At the other side of the spectrum is the development of full blown congestive heart failure with cardiomegaly, gallop rhythm, and myocardial irritability. The newborn infant, like the suckling mouse, appears to be especially vulnerable to a more fulminant course which is often fatal. In the adult the initial inflammatory response usually subsides and complete healing occurs, whereas in others signs of injury persist and a chronic phase of the disease evolves.

This transition from acute to chronic disease is not a recent observation. One hundred and fifty years ago, Corvisart wrote discerningly: " . . . carditis has been known to become fatal in a very few days while in other instances, the most alarming symptoms disappear and a sort of convalescence is established . . . as a chronic organic disease is then perpetuated . . . ."[46] The striking similarities between chronic infectious myocarditis and the unexplained myocardial diseases have been emphasized by Silber, Woodward[7] and others.[11] They have also raised the intriguing consideration of an infectious agent acting as the common inciting stimulus.

Benign idiopathic pericarditis has

recognized for many years as a distinct clinical entity.[31] An unemphasized facet of this disease is the frequent involvement of the myocardium by the underlying process. This association is underscored by the electrocardiographic aberrations which are a reflection of injury to the epicardium. The pericardium, which has no inherent electrical potential, does not participate in these alterations. Many astute clinicians further point out that chronic myocardial disease may follow an illness in which pericarditis dominates the clinical syndrome. The rub, chest pain, and other stigmata of pericardial inflammation disappear and the patient is left with cardiomegaly and/or a ventricular diastolic gallop, either of which reflects residual myocardial injury.

The syndrome of benign idiopathic pericarditis is often mislabeled since many cases are being identified as viral in origin. Several types of Coxsackie B virus have been incriminated by association and appear to be the most frequent offender.[36,37,38] The prefix *benign* may also be inappropriate for reasons alluded to earlier. In all likelihood the degree of myocardial involvement is the critical determining factor in the assessment of the *ultimate prognosis* in these patients, although pericardial constriction and effusion may rarely pose a serious problem.

The treatment of viral myocarditis is at present supportive and symptomatic. More definite therapeutic measures await a better understanding of the mechanisms of injury. Steroids have been utilized with variable results. Kilbourne[42] has shown that the giving of cortisone to the adult mouse recently infected with the Coxsackie B Type 3 virus resulted in extensive myocardial necrosis. The obvious inference is that steroids may be detrimental during the acute, toxic phase of the illness. However, an extension of this study in the postinfectious phase would be helpful. If delayed hypersensitivity plays a major role in the development of human myocarditis, it is reasonable that the antiallergic action of steroids may be useful during this latter period.

The microscopic changes in acute viral myocarditis are not unlike those described by Fiedler over 60 years ago in 4 well studied cases: Interstitial tissue is densely permeated with nests of mononuclear leucocytes. . . the muscle fiber shows swelling and decay of the cross bands. . . the nuclei are usually conserved but at times are swollen and stained more intensely than normal. . . within the musculature there are areas of necrosis. . . .[43] Recently these changes have been described in both infants and adults dying of fatal myocarditis, and are in general agreement with Fiedler's description, including the alteration of architectural structures and the intense interstitial exudative response. Since pathologic studies are lacking, knowledge of the changes that follow in the mild form of the disease is contingent on a better understanding of its pathogenesis. It is obvious that in most instances, the inflammatory response subsides without residual. However, when the process is severe, healing occurs, but normal myocardium is replaced by fibrosis and cicatrix formation, which, if extensive enough, may compromise efficient cardiac performance. Again, the degree of injury may be subclinical until some other process, i.e., coronary artery disease, superimposes itself. It is obvious that a better understanding of the mechanisms of injury will clarify many of the tangential problems with which we are now grappling.

One of the most tantalizing problems facing the investigator is the discovery of the etiological factor or factors responsible for the development of idiopathic disease of the myocardium. In the past, this syndrome has masqueraded as a whole constellation of synonyms, including idiopathic myocardial hypertrophy,[33] endocardial fibrosis,[44] chronic pernicious myocarditis,[45] the noncoronary cardiomyopathies,[47] and many others.[4] When stripped of nomenclature, and when the clinical and pathologic features are carefully assessed, it appears that each has *many* striking features in common with the others. Therefore, it is not unreasonable to suggest that at least some of these *syndromes* share in common the same inciting factor. Indeed, it is conceivable that many of these patients may have had a *mild* or forgotten viral illness, so that their condition represents an indolent form of burned-out myocarditis.[46]

What evidence is available to support the thesis that infectious myocarditis has inherent immune implications? Several clinical observations strongly suggest such a consideration. The delay between the initial infection and the expressions of cardiac disease has been a recurrent observation and mimics that seen in rheumatic fever.[67] In addition, the "hypersensitivity setting" has been noted in human disease and experimental animals which would suggest that an allergic diathesis is necessary. Heart disease of obscure origin which is found in several members of the same family may indeed represent examples of the occurrence of chronic myocarditis in a family who have been exposed to a common agent and who have a common immune response. Finally, the very mild infection elsewhere in the body may result in profound cardiac disability, a distinct characteristic of an antigen-antibody reaction.

The body normally cannot be tricked into making antibodies which will turn on itself. It is conceivable, however, that in the presence of an "adjuvant-like substance," there is a change in the antigenic properties of the heart. Adjuvant may not only alter this "recognition of self" but may also intensify the injury and potentiate the allergic response. It has been suggested that the infectious agent, particularly the virus, may act as an "adjuvant-like substance," and in this capacity modify the antigenic properties of the heart and set in motion a self-destructive process.

The usual viral illness is self-limited and does not recur unless immunity is lost. Should the virus in some way alter the host's own antigenic properties, the immune state may persist, or at least exacerbate after an anamnestic stimulus, giving rise to a disease which is chronic, progressive, or remittent. The observation of recurrent flare-ups in patients with chronic myocarditis after repeated respiratory infections makes this concept tenable.

This reaction rests on the premise that the heart will elaborate an antigen which will call forth an organ-specific antibody. Antiheart antibody has been demonstrated in several clinical settings, including the postcommissurotomy syndrome in rheumatic fever, in rheumatic heart disease, and after an acute myocardial infarction.[65] In this laboratory, circulating antiheart antibodies have also been found in a large percentage of patients with idiopathic myocardial disease. However, it is generally conceded that these antibodies demonstrated by both agglutination studies and by the immunofluorescent technique are an effect of injury rather than its cause. In addition, it is generally accepted that viral diseases induce a delayed type of sensitivity. In this setting, antibodies could only be identified through the passive transfer of lymphoid cells which are known to be the active mediators of delayed allergy of the tuberculin type. At the present time passive transfer has been accomplished in only three experimental models, i.e., autoimmune nephrosis,[67] experimental thyroiditis,[68] and allergic encephalomyelitis.[69-71]

The presence of circulating antiheart antibodies has been demonstrated in the experimental animal after the injection of both heterologous and homologous antigen. Kaplan[7, 72] demonstrated them in the rabbit after the innoculation of beef heart extract. Others have confirmed the development of antibodies in heterologous species and reaffirmed the observation that this antigen is indeed organ-specific.[73] In addition, these antibodies have been found to have a cytopathic effect on heart tissue cell culture.[73]

The production of antibodies through homologous heart extract has been more exacting. Cavalti[7] reported the development of autoantibodies in rats when used in conjunction with killed streptococci. This work has not been confirmed. Gery and Davies[75] could produce antibodies in 4 of 20 rabbits with homologous extract incorporated in Freund's adjuvant. These studies suggest the apparent necessity of adjuvant as an inciting factor. In addition, it appears that only the "receptive" or "hypersensitive" host will respond to this antigenic stimulus. Again it is to be emphasized that circulating antibodies may have little to do with initiating or perpetuating the disease but rather only reflect the host's response to injury.

The failure to produce myocarditis

with homologous heart antigen in experimental animals may be accounted for by one of several explanations (1) antibodies of the delayed type are not circulating and therefore would be undetected by serological methods (2) antibody response to myocardial changes may have been assessed too soon after the innoculation of antigen (3) an infectious agent plus homologous antigen and adjuvant may be needed to initiate potentiate and/or perpetuate the hypersensitivity phenomena.

The virus may initiate a deleterious antigen antibody reaction through still another mechanism. Recent excitement has been generated by Kaplan's observation that a common antigen exists between a partially purified protein component of the streptococcus and a constituent of the myofibers which will stimulate a cross-reacting antibody [7, 79] In rheumatic fever an autoimmune reaction may be induced in the human heart through exposure to cross-reacting antibody arising in response to Group A streptococcal antigen It is conceivable that other microorganisms as the virus, may also contain a common antigen with cross-reacting antibodies capable of setting off a hypersensitivity reaction

Strong inferential support for the autoimmune theory could be supplied by the confirmation of fixed gamma globulin within the myocardium of these patients. Kaplan utilizing the immunofluorescent technique has found bound gamma globulin in the atrial appendage of patients with rheumatic heart disease. The deposits were generously scattered throughout the atrial wall but predominantly involved portions of the sarcolemma and on occasion the interstitial connective tissue and endothelium of small vessels. In a similar study on patients with idiopathic myocardial disease, using antigenic material obtained at biopsy we were able to demonstrate the presence of bound gamma globulin in 4 of 7 patients, and the distribution of this protein was generously concentrated in the sarcolemma and subsarcolemmal areas. In a fifth patient, the walls of small blood vessels stained intensively with the fluorescent dye [66] The implications of these findings are not completely clear and do not necessarily imply that this is an immune process. However the presence of bound gamma globulin in the wall of ventricular muscle is highly suggestive and encourages a more concentrated attack on this problem. Meanwhile the assumption that the virus may initiate an autoimmune phenomena and that many examples of unexplained myocardial disease are related to an old viral infection is speculative and awaits further study

Summary

Many infectious agents may invade the heart and initiate an inflammatory process. The virus appears to be a frequent offender and its role in the production of both acute and chronic myocarditis is emphasized

The striking similarities, both clinically and pathologically between chronic infectious myocarditis and a large group of unexplained myocardial diseases are stressed and the possible relationships are discussed

The role of autoimmunity in the development of viral myocarditis is placed in current perspective

The treatment of the disease is at present symptomatic and supportive Specific therapy awaits a better understanding of the mechanisms of injury

The consideration that infectious myocarditis has immune connotations or that many instances of unexplained myocardial disease are related to old viral infections is conjectural and awaits further investigation.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Reserpine

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The rauwolfia alkaloids extracted from the snakelike root of the serpentine plant are now recognized as cardiac agents of considerable interest and therapeutic value. As with foxglove and chinchona, the rauwolfia alkaloids, which originated in India, had long been used empirically for a variety of ills. In the past decade, since gaining popularity in the Western world, a wealth of clinical and pharmacologic data has been accumulated. The most widely used alkaloid, reserpine, has been found to have a number of congeners with similar effects. Of these, syrosingopine, deserpidine, and rescinnamine have been most actively investigated. Definite clinical advantages, if any, over reserpine have not been demonstrated.

Pharmacologic effects

After the administration of reserpine the stores of serotonin in brain tissue, platelets, and the enterochromaffin cells of the intestines are depleted. Depletion of the levels of serotonin in brain tissue is an early effect which seems to correlate with the tranquillity induced by reserpine. Stores of catecholamine in heart muscle, brain tissue, adrenal tissue, and the arterial tissue are similarly depleted. The mechanisms of these effects and their relationship to the clinical usefulness of reserpine are obscure. However, it seems likely that the depletion of catecholamine in hypothalamic centers diminishes the control which these centers normally exert upon the sympathetic nervous system, allowing apparent increased parasympathetic influences. Thus fully reserpinized animals and animals with certain hypothalamic lesions may behave similarly.

Further sympatholytic effects of reserpine are probably secondary to a drug-induced reduction of peripheral sympathetic mediators. Apparently, under ordinary circumstances, such extensive depletion of stored catecholamine and serotonin has no adverse effect on patients or experimental animals. The effects on an organism under stress may be a good deal more apparent.

It is of clinical as well as experimental importance to note that reserpine may abolish the pressor responses to such agents as ephedrine and tyramine; infusion of norepinephrine will restore adrenergic responses.

These effects of reserpine are of particular interest when one compares the clinical response produced by reserpine with that of such recently introduced agents as alpha methyl-dopa and guanethidine. These agents also deplete the stores of catecholamine by different mechanisms and have different clinical effects.

Therapeutic value

When used in hypertensive patients, reserpine alone is of value primarily in treating mild labile elevations of blood

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pressure. A significant percentage of such individuals will become normotensive or approach normal levels. Unfortunately there have been few double-blind studies which compared the effects of reserpine placebo and mild sedatives. Long term control studies of morbidity and life expectancy in patients treated with reserpine are not available

In patients with more severe hypertension the use of reserpine in conjunction with other hypotensive drugs is of benefit Thus the combination of reserpine and chlorothiazide has been shown in double-blind studies to be more effective than either drug alone It is also often effective when used in conjunction with hydralazine in which case the reserpine tends to counteract the tachycardia that occasionally is produced by hydralazine. Reserpine when used in conjunction with a ganglion-blocking agent permits the use of a lower dose of the blocking agent. Here the parasympathomimetic effects of reserpine may be helpful in minimizing constipation. Parenterally administered reserpine in high dosage occasionally lowers blood pressure dramatically when used in treating patients during an acute hypertensive crisis.

Although reserpine has been advocated for slowing sinus tachycardia it is probably only helpful when the tachycardia is not secondary to organic disease.

The effects of reserpine in the hyperthyroid patient have occasionally been useful in the temporary control of acute symptoms, although the indications are not frequent At times, the manifestations of acute thyroid crisis may be reversed by reserpine.

The extensive studies on reserpine in the severely ill psychiatric patient suggest a distinct benefit from large doses. The precise role of reserpine in such therapy remains to be clarified

Side effects

When reserpine was first introduced in its unpurified form as rauwolfia, a number of observations were made which remain valid The drug has in small doses a delayed onset of action and similarly its effects persist for some weeks after discontinuation. There is a sedative component which in large doses seems to be effective in psychiatric treatment the smaller quantities of the drug used in the treatment of hypertension also produce some sedation and this effect must be taken into consideration in an evaluation of its efficacy in reducing blood pressure Reserpine diminishes sympathetic activity and therefore results in preponderant parasympathetic effects. Thus, bradycardia (only partially responsive to atropine) increased gastric secretion increased activity of the bowels myosis and nasal congestion may be produced The gastrointestinal effects may be hazardous in patients with a history of peptic ulcer Equally disturbing in some patients are recurrent nightmares, and large doses have been reported to produce Parkinsonism.

Although these side effects may be annoying more serious problems have been observed in patients undergoing long term therapy with reserpine. Severe mental depression with suicidal tendencies may occur particularly in those patients with previously demonstrated depressive tendencies and in those patients in whom high maintenance doses are used Careful evaluation of the emotional state of the patient should permit early detection of this potential danger

More recently it has become apparent that the stress of anesthesia and surgery in a reserpinized patient may produce prolonged hypotension and bradycardia. When these effects occur atropine will speed the heart rate slightly and norepinephrine will usually restore adequate levels of blood pressure. It should be noted that the synthetic pressor agents may not adequately reverse hypotension in some patients. Reserpine should be discontinued at least 2 weeks before elective surgery

Two other side effects should be kept in mind. Occasionally increased retention of fluid occurs in cardiac patients who undergo prolonged therapy with reserpine. Furthermore when reserpine is used in digitalized patients, a variety of arrhythmias may occur This effect has also been demonstrated in experimental animals and seems to be related to the depletion of cardiac catecholamine induced by reserpine. It is generally agreed that in order to minimize the side effects, no more than 0.25 mg of

reserpine daily should be used in long term antihypertensive therapy. Larger amounts in the first 2 weeks of treatment may be of value.

Summary

There is good evidence that hypertension, even of a moderate degree, is associated with a high incidence of vascular problems and probably a shortened life span. It is reasonable to assume that any drug which reduces the blood pressure may be beneficial. However, it must be kept in mind that there is, as yet, no evidence that reserpine therapy in patients with mild or moderate hypertension does indeed prolong life or lessen the frequency of the complications of high blood pressure. However, the drug is of unquestionable value in the therapy of hypertension and, occasionally, of other clinical situations when used with the appropriate reservations and caution. How reserpine lowers blood pressure—whether its effect is primarily on the central nervous system or on the peripheral sympathetic neurons—is still uncertain. Undoubtedly, when the pharmacologic effects of reserpine and similar catechol depletion agents are fully clarified, the clinical indications and value of these drugs will be extended.

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A rapid method for insertion of the pacemaker catheter electrode*

Heart block with Stokes-Adams seizures no longer has the shortened prognosis for life that it once held. Those patients who no longer are, or never have been amenable to medical management are now treated by artificial pacing with the intravenous endocardial catheter electrode or surgically implanted pacemakers.

The endocardial catheter electrode was employed first, therapeutically 3 years ago at Montefiore Hospital. Initially placed in a brachial vein it is now generally inserted through an external jugular vein at the base of the neck. Planned originally as a permanent installation, this device now has become the one of choice in any situation in which short term internal pacing is desired for therapy or research. It is safer and more comfortable in emergencies than prolonged external pacing, affords time in which to prepare such patient for future implantation of a buried unit, and diminishes the risk of accidents and arrhythmias during anesthesia and surgery.

Under normal circumstances, catheterization from the external jugular vein can be accomplished within 1 hour during which time patients with episodes of ventricular asystole can be controlled by Isuprel or external pacing. When the mechanism of syncope is ventricular fibrillation, or the patient is orthopneic or in shock this comfortable margin of time may be reduced sharply. In such patients, within 10 minutes from the time of positioning on the fluoroscope table to pacing, a No. 5 French electrode catheter has been passed into the inflow tract or apex of the right ventricle through a No. 13 thin-walled (No. 13T) needle inserted into the femoral vein.

The technique of needle positioning and the type of needle used are similar to those described by Seldinger[1] and Brockenbrough[4] for arterial puncture. The needle† is inserted just medial to the femoral pulse about 2 inches (in the adult) below the inguinal ligament and passed obliquely deep and cephalad until the vein is pierced. The cutting stylet is then withdrawn and the blunt outer shaft of the needle is threaded gently into the vein. When good blood flow is obtained, the catheter is passed into the needle up the femoral vein, and into the inferior vena cava. Once the catheter is ascertained to be in the vein, the needle is withdrawn over the catheter and further maneuvering of the catheter is done percutaneously. It is important to limit maneuvering of the catheter while the needle is still in place, since even the blunt edge of the needle may shave the finish off the tightly fitting catheter.‡ Once the catheter is in the inferior vena cava, the technique of placement of the electrode in the right ventricle is that of right heart catheterization through the saphenous vein.

A unipolar, bipolar, or dipolar electrode[4] catheter§ may be employed although with the latter two placement for pacing is easier. The unipolar catheter requires endocardial contact of the electrode and an indifferent skin electrode to complete the circuit. The bipolar or dipolar catheters do not require endocardial contact or indifferent leads and can be placed in mid-chamber diminishing the risk of apical myocardial perforation which may be present with a unipolar tip thrust deep into the apex of the chamber. The terminal heads of the electrodes prohibit complete withdrawal of the 13T needle over any of these catheters. In order to preserve the catheters, it has been the practice to leave the needle on the catheter at the terminal head and tape it, together with the pacer, to the anterior surface of the thigh. When the electrode is withdrawn, the needle is retrieved.

Hemostasis, after withdrawal, is normally achieved by 5 to 20 minutes of pressure over the site of puncture in the nonanticoagulated patient.

This technique of catheterization does not require destruction of the vein or affect its future re-use. It has been employed as the method of choice when it was known in advance that the patient would be undergoing surgery within the week, or when only short term pacing was anticipated. It has also been used in acute emergencies, in cases in which it was later replaced by an insertion into the jugular vein for prolonged maintenance. It has not been employed for long-term placement at this site be-

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†Special order supplied by Becton-Dickinson.
‡Newly designed Teflon-tipped needles (Becton-Dickinson) may alleviate this problem.
§No. C51 or C52, United States Catheter & Instrument Company, Glens Falls, New York. This make, on special order, dipolar catheters.

use of d fficulty in effecting ambulation of the patient nd the presumed increased ri-k of thrombophlebitis Anticoagulation is optional.

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Permanent implantable pacemakers in the treatment of complete heart block

The development of a number of completely im plantable ardia pacemakers of various types has been significant ad nce in the management of chronic complete heart block. Slightly over 3 years ha now elapsed since Chardack, Gage nd Greatbach first successfully implanted a transistorized fixed-r t pacemaker in a huma being Over 1,200 of these u it ar now in clinical use Kantrowitz and colleagues[1] ha developed and utilized a fixed-minimum-rat cont ol device. At such times when increased cardiac rat might be desirable this is accomplished by placing small induction coil on the km overl ing the internal pacemaker Control of cardiac pacemaker rat by radio-frequency stimulation has been utilized by Glenn nd associates The method affords an external means of arying the signal but has the disad antage of requiring cumbersome transmitting coil t be lway in proximity to the skin overlying the implanted receiving coil. The method seems promising and further investigation and simplification will assuredly result in wider use of this technique.

The battery life of the implantable units has not been clearly delineated but it is conservatively estimated t be approximately 5 ears. Early f ilure of batteries nd components has occurred, but, fortunately this has been rare. The over-all excellent predictability of the fixed-rate units to dat can be ascribed to the relativel few component in the subcutaneously implanted battery pack (eight to ten parts) and the superb improvement in electrode design. The Chardack-Greatbach electrode consists of a helical spring platinum-iridium alloy which permits both flexion nd elongation. Since this design was adopted, electrode failure has been almost nonexistent

Recently Samet and colleagues[2] ha e attention to the hemodynamic consequenc asynchronous idioventricular pacing as in a patient with implanted fixed-rat pacem When P-wave ctivity is discernible before maker and entricula electrical activity f arterial pressures rise nd right atrial pre fall. When the P wave is lost within ent electrical activity a large av develops atrial pressur curs This is consequent t traction of the trium on a partially or comp losed tricuspid val Moreover subst momentary fall in systemic arterial pressure t this time These cyclic changes in arterial sure ar synchronous with changes in the P temporal sequence When there is normal rel ship the arterial pressures rise when the P lost within the QRS complex, the pressure The importance of trial systole in the m nance of ventricular filling nd cardiac outpu been repeatedly emphasized by many auth One must conclude therefore that the most p logic type of pacing is of synchronous in which the normal P-QRS relationship is tained. N than and co-workers[3,4] ha e re described n ingenious impla table synch pacemaking unit hich picks up the negati tion of the P amplifies it, introduces delay pproximately equal t normal P ters l, and finally initiates ventricular de zation. Thus essentially normal electromech relationships between tria and entricles are tained. Alterations in atrial rate ill cau entricles t follow in a synchronous fash suitable blocking dev ice prevents excessively entricular rates should atrial tachycardia, f

r fibrillation occur. Some concern has been registered that the possibility of pacemaker failure is theoretically higher in the synchronous pacer since there are approximately [illegible] times as many components. Fortunately this has not been a problem to date.

At the present time a number of investigators are devoting considerable effort to perfecting a means of prolonging battery life and to deriving an electrical driving force of virtually limitless temporal span, using the piezoelectric principle. These developments will be eagerly awaited.

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The discovery of the augmented unipolar limb leads by R. H. Kahn in 1909

In 1909 R. H. Kahn of Prague described the leads now known as the augmented unipolar limb leads.

Kahn stated that there was the possibility of combining Einthoven's leads two at a time so that all three lead points were connected to the galvanometer. He stated that, of the conceivable combinations four were practicable: I + II, II + III, I − III, III − I. Kahn pointed out that the last two furnish an electrocardiogram which differs only in sign, and from a desire to obtain upright deflection he selected I − III.

Kahn named his leads IV, V, and VI; they were taken with one end of the string galvanometer connected to one extremity and the other end of the string connected to a wire leading to the other two extremity lead points. The relations between Kahn's leads, the so-called augmented unipolar leads described by Goldberger, and Einthoven's leads are as follows:

$$IV = -V = \frac{I + II}{2}$$

$$V = V = \frac{II + III}{2}$$

$$VI = V = \frac{I - III}{2}$$

Kahn stated that, in recording Lead IV, one was in effect simultaneously registering Leads I and II with the same sense or sign, and similarly for Lead V with regard to Leads II and III. He stated that the matter was not so simple with Lead VI. Electrocardiograms taken with these leads were illustrated and Kahn briefly described his experience with these leads.

If the recording of Kahn's lead had become standard in 1909, a large amount of effort expended in devising and evaluating the unipolar and augmented unipolar limb leads could have been avoided. More importantly, strong schools of unipolar thought might not have appeared. If the so-called augmented unipolar leads after their rediscovery had been viewed in accordance with Kahn as equal to combinations of Einthoven's leads, it seems unlikely that any one would have thought of them as far superior to Einthoven's leads, and surely no one would have viewed them as being basic leads from which Einthoven's leads were constructed.

If it were a relatively simple matter it ...

seem proper t... et n t the names proposed by Kahn for these lead since his names do not indicate important differences between the two sets of limb leads. ... et m s the names proposed by Kahn would be ... tribute not only t... his discovery of th... set of lead but tribute t his understanding of these lead...

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Problems in the evaluation of cardiovascular responses to inhalation of vasoactive substances

N... report has been published describing the ... ascular responses ... halation of ... substances such ... m l ... nd ergota... m ... tart ... from such studies may ha... qual... bility particularly ... hen the subject his ... ent ... However ... ttempt ... quantitat... responses t... halation of ... substances must be made ... tion particularly when variations among subject... compared.

Cardiovascular responses to drugs are dependent upon dosage. In fact, some drugs have exactly opposite effect... hen administered in small and large doses. When ... drug is administered by inhalation it is impossible to be certain of the amount of the drug which has actually entered the circulation. Even if the dose delivered by the nebulizer is carefully controlled the amount of the drug which enters the alveolar spaces must vary a great deal among individuals. For example, in older subjects with senile emphysema or ... subject with obstructive emphysema ... ariation in effective tidal volume greatly alter the amount of drug which reaches the circulation. Furthermore, in patient... with obstructive emphysema or pulmonary fibrosis the drug may enter poorly vascularized alveoli and under such circumstances it would not enter the circulation. These considerations are of particular importance when two groups of people of different ages and different states of health are being compared. The higher natural incidence of senile and obstructive emphysema in older people than in younger people would result in systematic error in estimations of dosage. This error could well result in erroneous interpretation. The same considerations apply to the comparison of patients with and without heart disease. It is well known that congestive heart failure is associated with decreased lung compliance. Thus, any group of patients with heart disease may include patients with varying degrees of ventilatory restriction. An attempt to evaluate the effect of ... substance delivered to the circulation by inhalation on such phenomena ... the characteristics of ... murmur, peripheral blood flow, or pulse contour must be associated with variations due to effective dosage differences rather than differences in physiologic response.

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Book reviews

DIETARY CONTROL OF HYPERCHOLESTEREMIA. By Dorothy Tompkins Revell, Therapeutic Dietitian, A.D.A. Dakota Clinic, Fargo, N. D., with Gerald J. Kavanaugh, M.D., Section of Internal Medicine, Dakota Clinic. Springfield, Ill., 1962, Charles C Thomas, Publisher. 70 pages. Price $4.50.

This is a diet manual for the use of physicians or patients when it is considered desirable to prescribe or follow a diet high in polyunsaturated fat. The diets which are described vary in energy value from 800 to 2,200 calories including one that is unrestricted in calories. Fat furnishes approximately 35 per cent of the calories with a ratio of one part of saturated to two parts of unsaturated fat. Protein supplies 25 per cent and carbohydrate 40 per cent of the remaining calories. The diets are planned using the food exchange method which was developed some years ago for dietary therapy of patients with diabetes mellitus. The diets which are low in calories should be useful in the treatment of obesity. Those of higher calorie value are similar to diets which have been shown to be effective in reducing elevated serum cholesterol concentrations in many subjects. The manual also contains diets high in polyunsaturated fat for the treatment of peptic ulcer. The diets and exchange lists are clearly outlined and a number of recipes for the preparation of foods without saturated fat are given. An undesirable aspect of the menu plan in all of the diets is the inclusion of unsaturated vegetable oil at breakfast in amounts of three teaspoons to two tablespoons, taken alone or mixed with fruit juice or skim milk. In some of the diets, a vegetable salad is suggested twice daily but without any salad dressing. The oil might better be used for this purpose. Many patients will find oily drinks at breakfast unpalatable. All of the diets include uncreamed cottage cheese, and diets of 1,200 calories or more include three to five cups of skim milk, a rather large amount. Unfortunately, the only exchanges given for the skim milk are buttermilk (made from skim milk) or powdered nonfat milk. This may preclude use of the diets by some patients. With these exceptions, the diets are practical and varied, and the manual should prove to be useful for its avowed purpose.

THE STRESS OF LIFE. By Hans Selye, M.D. New York, 1963, McGraw-Hill Book Company, Inc. 324 pages. Price $2.75.

This is one of the summaries of the many years of study and the thought of Hans Selye. His ideas and findings are presented in relatively simple terms both for the professional and the layman. The latter may find the book both difficult, between the serious scientist will find it interesting but surely incomplete and at times superficial. Selye has been a constant proponent of the concept of stress as a cause of disease and, of course, has often oversimplified disease mechanisms. His contributions are important, as is evident from this book.

Selye has divided his presentation into 6 books. Book I is concerned with the discovery of the concept of stress. Book II analyzes the mechanisms of stress-producing situations. Book III presents disease of adaptation in which the body fails in stress-fighting mechanism. Disease states discussed include those of the heart and circulation, kidneys, central nervous and endocrine systems, and gastrointestinal tract. Book IV synthesizes the concepts of stress in order to provide a unified theory of diseases of adaptation so that they may be better understood and managed. Book V presents implications and applications of these ideas on stress.

This work is recommended for profitable reading and as a single source of Selye's ideas. Regardless of one's opinion of Selye's studies, the importance of them cannot be denied. They need serious consideration by all biologists, especially those interested in medicine and man's behavior and his diseases. There are fairly good illustrations to support the discussion. The book is a paperback, not expensive, and well written to present Dr. Selye's concepts.

ADVANCES IN CARDIOPULMONARY DISEASES. Volume 1. Edited by Andrew L. Banyai, M.D., and Burgess L. Gordon, M.D. Chicago, 1963, Year Book Medical Publishers, Inc. 359 pages, 96 illustrations. Price $11.

This book is composed of lectures given at the postgraduate courses of The American College of Chest Physicians during the year 1961. The subject matter and quality of the material presented varies considerably but persons in most clinical fields will find something of interest in this monograph. Dr. Hurley Motley discusses oxygen transfer and Dr. David Cugell covers alveolar and dead-space ventilation, both of which subjects are lucidly presented. A topical discussion of air pollution is given by Dr. G. W. H. Schepers. He uniquely separates harmful environmental agents by their effect on the anatomic divisions of the respiratory apparatus. An interesting and refreshing chapter by Dr. David Spain includes discussions about such newer pulmonary entities as pulmonary alveolar proteinosis and thesaurosis, and such relatively uncommon conditions as pneumocystis carinii pneumonia, pulmonary eosinophilic granuloma and pulmonary hemosiderosis. The above-mentioned conditions are discussed in relation to their interest to industry.

The chapter concerning chronic bronchitis and emphysema seems to be somewhat superficial and at times misleading, particularly in regard to the management of these conditions.

Dr. Henry Swan provides an informative review of the repair of congenital

ardiac lesions and an i teresting treatment of dissecting neurysm of the aorta is gi en by Dr Johns nd Dr Hu t

This monograph is of necessity a pretty review of ad nces rdiopulmonary dise ses but t n be d th onsider ble profit by the medic l student or pract ing ph sician.

BIRTH DEFECTS Ed ted by Morris Fishbei M D w th 31 eminent ontributors Philadelphia, 1963 J B Lippinc tt Compan 335 pages Pri $5

This book edited by Morris F shbein nd sponsored by the N tional Foundation, is ttempt t g ther together summarized form the current knowledge oncerning the broad topic of birth defect The olume ha 31 distinguished con t butor Birth defect are on idered in gener l in terms of frequency causation, prevention and treatment In add tion historical review l the impact of such defects on the hild, his f mil and on society re included Separat hapter are devoted t gener l genetic genetic counselling nd t the l t hromosomes nd their molec la structure Recognized causes of congen t l defects, such hromosomal aberra tion adiation nd iruses re onsidered There 8 hapter dev ed t spec fic defects.

There perhaps someth ng for everyone i this book A stated by Dr Apgar the preface it is intended t provide sou of information nd explanation for pa ent of hildren th birth defect For the rdiologist or pediatric rdiologist there hapter by Dr T ussig on ongen tal cardiac defect This is written specifically for parent of children ith congenital heart disease to offer general explanation of such cardiac defect nd genetic counselling i regard t them.

There i little that is eally new nd no intensive exploration of given topic ppears. The book as stated is intended for parent as well as ph sicians nd accumulated knowledge such as it is in regard t congenital bnormalities, is put nder one cover nd considered from several aspects by those ell qualified in the field.

RESUSCITATION AND ARTIFICIAL HYPOTHERMIA By V A Negovskii, with preface by Claude S Beck M D New York 1962 Consultants Bureau Enterprises, Inc. 314 pages. Price $12 50

This is n interesting book which ill be particularly useful a reference text because of its extensiv bibliography It is, however ery difficult to read. From the standpoint of quickl acquiring the facts of clinical resuscitation one would find it of much more dva tage t consult the wall charts recently prepared by the American Heart Association than to ttempt t get them by wading through the mass of ord contained in this volume Nonetheless, this criticism should not detract at all from one of the most useful features of this book. The uthor has summarized in very comprehensi fashion the results of his own experimentation, s w ll a the results of virtually ll other significant experimentation, in the field of resuscitation from cardiac nd respiratory arrest It is simply unfortunate that the det il of clinical management are scattered throughout the work. This book would be of considerable alue to nyone planning t in estigate experimentally ny spect of the resuscita tion problem. In add tion, the bibliography af ford some knowledge of the history of experience with resuscitation after cardiac and respiratory arrest The text incidentally is ery attractively printed bound and illustrated.

SPECIÁLNÍ KARDIOLOGIE II By Prof Mudr Vratislav Jonas Praha, Czechoslov kia. Praha 1962 Stat i Zdra otnické Nakladatelství, 656 pages, 181 illustrations.

This second olume of Vratislav Jonas monograph on rdiology published i 1962 contains an enormous mount of aluable information about pericarditis nd myocardial disease More tha 250 pages re dev ted to pericarditis alone, really monograph in itself and another 300-odd pages to myocardial disease In addition, there i section on neoplasms of the heart. Illustrations abound nd include man electrocardiogram and x-ra pict res nd ho photographs of pathologic specimens.

The great ariety of etiological types of pericarditis nd myocarditis is clearly evident in this olume

The uthor ha searched the orld l terature i great detail nd has selected excellent bibliographies which are added t the end of all three sections.

A English translation of this book would be of value

ELEMENTI DI ANATOMIA GENERALE E DI EMBRIOLOGIA DEL CUORE, DEL PERICARDIO E DEI VASI SANGUIFERI. By Francesco Loreti, Professor (Ordinario) of Normal Huma Anatomy Universit of Turin. Naples, 1963 Casa Editrice Idelson di E. Gnocchi F 313 pages 109 figures. Price 8,500 lire

This ol me according t the author statement in the preface was designed as reference ork for medical student nd physicians, nd, in particular among the latter cardiologist and cardiac surgeons. Its general coverage is indicated i the title

There re nine chapters. I General principles of the circulation of blood and lymph (6 pages). II Heart (125 pages) gross anatomy minute anatomy histology changes ith aging, blood and lymph essels, nerves, topography III Pericardium (23 pages) gross natomy relations, vessels, nerves IV Arteries (43 pages): distribution, nastomoses, histology essels and nerves, variations, arteriovenous anastomoses. V Blood capillaries (21 pages) generalizations histologic

structure, nerves. VI. Veins (25 pages): distribution, anastomoses, valves, histology of venous walls and valves, vessels and nerves. VII. Histogenesis and morphogenesis of the heart, pericardium, and blood vessels (20 pages). VIII. Fetal circulation and the remnants of temporary fetal vessels (9 pages). IX. Historical outline of studies on the blood-vascular system (16 pages).

The bibliography is divided into four sections, placed in appropriate relation to chapters, occupying in all about 13 pages that are not counted in the above-mentioned paginations. Although some expected key references are missing, the bibliography is comprehensive enough for the purpose and reasonably representative of the international literature. Both subject and author indexes are provided. The illustrations (a large share of them original with the author) are well chosen and instructive. The text is succinct. The author's sense of history is admirable. In addition to the historical chapter he repeatedly presents such comment in footnotes, and most of the chapters are headed by pertinent quotations such as this one from Aristotle that opens the chapter on the heart: "Cor principium sensuum, et motus et vitae."

The book should well serve its intended purpose for those acquainted with the Italian language.

Heparin: Metabolism, Physiology and Clinical Application. By Hyman Engelberg, M.D., Attending Physician, Cedars of Lebanon Hospital, Los Angeles, Calif.; with Kenneth D. Brown, Ph.D., Veterans Administration Hospital, Downey, Ill. Springfield, Ill., 1963, Charles C Thomas, Publisher. 218 pages. Price $8.50.

The first portion of this monograph consists of a review of the basic chemistry, metabolism, and action of heparin. The second portion consists of a review of much of the literature concerned with the clinical applications of heparin. Considerable emphasis is given to the lipemic-clearing action of heparin. The bibliography is extensive. In view of the voluminous literature and conflicting reports one may justifiably question the value of the necessarily superficial review presented in this small monograph. This reviewer would welcome a more critical analysis of several of the better reports, with an attempt to resolve some of the points of conflict on the basis of the author's own extensive work in this field. The book is well written and easy to read. The printing and binding are of good quality. This volume may serve a useful purpose as a ready although superficial reference source for those clinical and laboratory investigators interested in heparin.

Thoracic Surgical Management. By J. R. Belcher, M.S., F.R.C.S., Surgeon, London Chest Hospital, Thoracic Surgeon, Middlesex Hospital; and M. F. Sturridge, M.B., B.S., F.R.C.S., First Assistant, London Chest and Brompton Hospitals. Baltimore, 1962, Williams & Wilkins Company. 211 pages. Price $7.

This book is intended primarily to inform students and those physicians who are beginning the practice of thoracic surgery. As a primer of thoracic surgery it is most useful in providing the principles, methods of diagnosis, and treatment. The book is arranged in organized outline form to present the various topics in a concise manner.

In the third edition the cardiac aspect of thoracic surgery is a welcome addition. Because the book is designed to orient those starting in thoracic surgery, the authors have wisely omitted the techniques of cardiovascular surgery which are continuously changing and which are often obsolete by the time of the first printing. Emphasis is placed on the diagnostic methods and the preoperative and postoperative care of the patient undergoing cardiac surgery.

Many illustrations help to teach the fundamentals of thoracic surgery. Comprehensive and concise, this book should be immensely valuable to the busy surgical resident who is required to pursue multiple disciplines.

Announcements

The Mount Sinai Hospital of Greater Miami is offering a Postgraduate Course in PHYSIOLOGY AND PATHOPHYSIOLOGY IN CLINICAL CARDIOLOGY by James V. Warren, M.D., of Ohio State University, Columbus, Ohio, from November 18 through November 22, 1963. Evening sessions will start at 8:00 P.M.

Direct inquiries to Victor H. Kugel, M.D., Chief, Cardiovascular Section, Department of Medicine, Mount Sinai Hospital of Greater Miami, 4300 Alton Rd., Miami Beach 40, Fla.

THE WESTERN SOCIETY FOR CLINICAL RESEARCH will hold its Seventeenth Annual Meeting in Carmel-by-the-Sea, California, on Wednesday, Thursday, Friday, and Saturday morning, January 29-31 and February 1, 1964.

Information about the meeting may be obtained from Dr. Homer R. Warner, Secretary-Treasurer, Latter Day Saints Hospital, 325 Eighth Ave., Salt Lake City 3, Utah.

A SYMPOSIUM ON DIFFERENTIATION AND DEVELOPMENT, the Fifth International Basic Science Symposium of the New York Heart Association, will be held in New York City at the Biltmore Hotel, Friday and Saturday, Feb. 7 and 8, 1964.

For information on registration, write to the Symposium Committee, 10 Columbus Circle, New York 19, N. Y.

A CONFERENCE ON COMPARATIVE ATHEROSCLEROSIS (SPONTANEOUS AND EXPERIMENTAL), sponsored by the Council on Arteriosclerosis of the American Heart Association and by the Los Angeles County Heart Association, and supported in part by the National Heart Institute, will be held on January 30 and 31, 1964, at the Beverly Hills Hotel, Beverly Hills, Calif.

Registration is limited to 300 and a registration fee of $10 per day ($20 total) will be charged.

For information write to Mrs. Elizabeth McCandless, Los Angeles County Heart Association, 2405 West Eighth St., Los Angeles 57, Calif.

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Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year

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Editorial

The caliber of the retinal arteries in hypertension

F B Byrom M.D
London England

It is still a common error in medicine to neglect the tempest and sit brooding over the wreckage it leaves in its wake. Malignant hypertension is a case in point It is widely assumed that the symptoms and signs of the disease are caused by its typical lesion—a complex mixture of necrosis, hemorrhage aneurysm formation and cellular proliferation in or around scattered terminal branches of the systemic arterial tree. The lesion is probably more chronic than it looks, and given time, it can cause irreparable damage especially in the kidney But in the early stages of the disease although the patient is seriously ill the lesions may be very inconspicuous, and they are evidently only the wreckage of a less obvious but more widespread and reversible morbid vascular disturbance. This disturbance can be studied in detail in the rat with severe hypertension caused by constricting the artery to a solitary kidney[2] with a simplified Goldblatt clamp. Exteriorization of the kidney should be avoided because it causes perinephritis. In an earlier study[3] at St Vincent's Hospital Sydney it was found that when such rats developed acute cerebral symptoms the typical lesions of malignancy were rather inconstant in the brain and were overshadowed and heavily outnumbered by zones of increased capillary permeability and focal edema and by wide spread diffuse and focal constriction of the cerebral arteries. When the hypertension was abolished by removing the clamp the arteries quickly reverted to normal and the symptoms disappeared within a few hours—long before any structural lesions could have healed

In a more recent study[4] in this department the changes in arterial caliber have been examined more closely in a more accessible extension of the brain, the retina using a 300-year old technique[5] which calls for nothing more than a dilated pupil a coverslip over a drop of saline in the conjunctival sac and a magnifying glass or dissecting microscope. Although hemorrhage, edema retinal detachment, and exudates were occasionally seen the most interesting change observed in severe hypertension consisted of more or less localized zones of narrowing of one or more arterioles, the rest of the artery being normal or dilated This striking change sometimes appeared early especially in rats with acute encephalopathy But more often it developed very gradually over a period of weeks or months. In either case the irregularity was remarkably persistent varying little in degree and not at all in position. Such changes have been described before in the rat the dog and man and they have been and still are attributed by some[6-8] but not all [11,12] observers to

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progressive anatomic narrowing. But appearances are deceptive. In the rat it has been found that, with a few exceptions, the change in caliber can be rapidly reversed. In recent cases even extreme narrowing will usually disappear within a few minutes if the level of ether anesthesia is deepened, and will reappear always in the same places if the ether is suspended. In time the constrictions gradually become refractory to ether, perhaps because of muscular hypertrophy—but they can still usually be abolished promptly and permanently by removing the clamp from the renal artery. This demonstration that in the rat with chronic renal hypertension reversible vasoconstriction can accurately mimic focal anatomic narrowing confirms earlier conclusions in the dog and strongly supports the view that the essentially similar changes in human renal and malignant hypertension are equally labile. Some focal organic narrowing undoubtedly occurs but, paradoxical though it may seem, it is structural change and not spasm that should be logically suspect in a narrowed retinal vessel.

The changes in the retinal arterioles closely resemble those recorded in the cerebral arteries in rats with acute encephalopathy, and strongly suggest that the latter changes were genuine hypertensive phenomena and not artefacts related to cranial windows or cerebral edema. It seems that in the severer grades of hypertension, or at least renal hypertension, there is a tendency for diffuse hypertonia of the systemic resistance vessels to be gradually overlaid by a more complex mixture of constriction and dilatation. Plain muscle fibers are not distributed evenly along the length of these vessels, and the irregularity may simply mean that under the stress of excessive filling tension too rapidly applied only the more muscular zones of the artery can withstand the pressure and undergo hypertrophy, whereas the weaker regions become overstretched. An even steeper rise may account for the occasional finding in the rat of general dilatation and marked tortuosity of the retinal arterioles. On the other hand a more gradual rise may allow the weaker regions of the vessels to hypertrophy and so maintain uniform vasoconstriction which even in severe hypertension is more common than focal narrowing.

So much for the nature of the change. Its significance is debatable. The retinal appearances leave little room for doubt that the earlier or milder grades are harmless. If the more severe grades are accepted as responsible for the symptoms, the focal edema and structural lesions of malignancy, the problem remains of whether it is excessive constriction (spasm) over dilatation or a combination of the two that is injurious. On the whole opinion has favored spasm. In 1905 Pal[12] described transient local vascular disturbances usually preceded by steep rises in pressure in hypertensive patients and because of the fleeting nature of these vascular crises he attributed them to brief local arterial spasm provoked directly by excessive filling tension.[13] Later Volhard,[1] in developing the concept of malignant hypertension, attributed the signs and symptoms of the disease to a more chronic form of spasm. In animals a number of unrelated renal vasoconstrictors, including vasopressin,[15] oxytocin,[6] serotonin,[17] methoxamine, and angiotensin, cause atypical medial necrosis of *large* renal and other arteries when given in very large doses. But in renal hypertension, although focal constriction may be very severe, no local reduction in blood flow has yet been demonstrated and the possibility[19] that the less conspicuous dilatation may cause the damage cannot be excluded. Nevertheless certain firm conclusions can be drawn. The first is that excessive filling tension is the main if not the sole damaging agent since lesions do not occur distal to a Goldblatt clamp.[1] The second concerns the possible role of accessory factors. Like any other biologic process the development of lesions may be modified by many factors natural or artificial. X-irradiation, for instance, predisposes arteries to lesions,[22] and it is remotely possible that it does so by destroying vasomotor nerve endings,[23] in the absence of which the reactivity of the vessels to certain polypeptides[24] and perhaps other vasoconstrictors is increased. Any *essential* accessory factors[25] must belong, however, to the hypertensive process rather than to the subject, since the damage can be arrested by removing the clamp.

But the most important inference is that malignancy is essentially a labile state. In the experimental model complete and very rapid reversibility even after many months is ensured by the solitary kidney protected as it is by the clamp against secondary hypertensive damage. In man the presence of two kidneys complicates the situation and until kidney grafting is perfected dramatic reversal is to be expected only in the rare cases of *strictly* unilateral renal hypertension in which it is possible *completely* to correct renal ischemia *without damaging or removing normal renal tissue*.

Even more common than patchy irregularity of caliber in the hypertensive rat is a change described in man by Gowers[25] nearly 90 years ago namely diffuse narrowing of the retinal arterioles in proportion to the rise in arterial tension. Although in the present experiments the constriction was found to be rapidly reversible the life span of the rat is too short to permit any comparison with changes in benign essential (as distinct from malignant renal) hypertension in man. But apart from cerebral and coronary vascular catastrophes it is all too often assumed that given time the disease will become irreversible because labile vasoconstriction has turned into rigid arteriosclerosis. There are good reasons for resisting this pessimistic view. First retinal appearances which are largely responsible for the idea are as we have seen misleading and arterioles which look like copper or silver wire are not necessarily rigid. Secondly life to the circulatory system is a matter of endless balancing of regional arteriolar tone and a man whose arterioles had all turned rigid enough to fix his hypertension would one may suspect drop dead if he stood up. And finally there is no convincing evidence experimental or clinical that hypertension ever becomes irreversible except when it derives from or has itself caused incurable renal ischemia. [26]

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Clinical communications

The effect of exercise on cardiac performance in human subjects with congestive heart failure

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The stress of exercise has long been used as a means of uncovering or exaggerating physiologic abnormalities of the circulatory system. Numerous studies in patients with congestive heart failure have characterized defects in delivery of blood flow, ventricular filling pressure, tissue oxygen supply, and a number of related measurements. On the other hand, relatively few observations have been made on the nature and magnitude of the energy requirements of failing hearts in the resting state and during physical exercise.

Bing, Blain, Lombardo[3] and their respective co-workers reported myocardial efficiency to be subnormal in the failing heart at rest and also during exercise. Although the mechanical efficiency of the normal heart increases with effort, Gorlin and associates[4] found that it remains unchanged in patients with congestive heart failure. Furthermore, Levine and Wagman found that the oxygen cost of the generation of pressure was abnormally great in the failing heart subjected to the stress of physical exercise.

It is the purpose of this report to describe in detail the patterns of myocardial energy requirements and supply in a group of patients with congestive heart failure studied at rest and during physical exercise.

Materials and methods

Catheterizations of the right side of the heart and the coronary sinus were performed in 19 subjects with left ventricular failure. All were in clinical Classes III or IV, C or D.† All demonstrated clinical evidence of congestive heart failure, and in each, pulmonary capillary or left ventricular end-diastolic pressures were greater than 12 mm. Hg at rest and/or greater than 16 mm. Hg during supine leg-raising exercise. This group included 2 patients with coronary sclerosis, 3 with rheumatic mitral insufficiency, 6 with aortic insufficiency, 4 with aortic stenosis and insufficiency, and 1 each with aortic stenosis, subaortic stenosis, hypertensive heart disease, and left ventricular failure of unknown etiology (Table I). None of these subjects had obstructive mitral valve disease or were in atrial fibrillation at

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†All were on maintenance digitalis preparations.

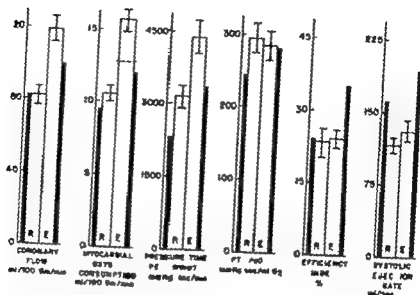


Fig. 1. The open bars represent mean values and their standard errors for the major parameters of myocardial function at rest (*R*) and during exercise (*E*). The thin solid bars represent control values for comparison. The two groups (control and congestive failure) increased pressure-time per minute to approximately the same degree on exercise, yet myocardial oxygen consumption rose much more in the failure group. This occurred despite the fact that the muscle mass of the failure group available to develop pressure was at least 35 per cent greater than in the controls. The dashed line on qO_2 depicts the theoretical increment required per 100 Gm. of the increased muscle mass (12.8 ml./100 Gm./min.). This again emphasizes the increased energy cost of the failing myocardium during exercise (15.1 ml./100 Gm./min.)

the time of study. Sixteen subjects with normal left ventricles described in detail elsewhere served as a control group.

The methods utilized in this study have been described in a previous paper. In addition to catheterization of the right side of the heart, catheterization of the left side of the heart was performed in those patients with aortic valve disease and whenever aortic stenosis was present left ventricular systolic pressures were used for all derived calculations at rest except as specified. During effort in those patients, left ventricular systolic mean pressure was calculated hydraulically from the calculated aortic valve area.[8] In those subjects without aortic stenosis, brachial arterial pressures were used for all calculations which involved left ventricular dynamics. Cardiac output refers in each instance to *effective* cardiac output, irrespective of the presence or absence of valvular regurgitation. Thus, stroke index, stroke power, left ventricular work index, mechanical efficiency index, and mean systolic ejection rate are all derived from effective and not total flow rates.

Results

Tables I and II show data obtained during catheterization of the pulmonary artery. The total body oxygen consumption index was 13 per cent higher at rest in the subjects with failure than in the control subjects ($0.01 < p < 0.025$) but rose a comparable percentage (122 and 129 per cent, respectively) on exercise. Resting cardiac index was significantly decreased ($p < 0.01$) relative to the control subjects and rose less on effort. The average resting systemic arteriovenous oxygen difference was 1.9 volumes per cent greater in the subjects with failure than in the control subjects and widened an average of 1.1 volumes per cent more during effort than in the latter group.

Resting effective stroke index was low and did not change during exercise. Mean effective systolic ejection rate was low at rest and did not rise significantly (0 2 < p) on effort (Fig 1). The observed increase in cardiac output was mediated entirely by heart rate. Both left ventricular work index and stroke power rose on effort although to a somewhat lesser extent than in the control subjects. Systemic vascular resistance was higher at rest than in the control subjects and fell less during exercise. The average pulmonary capillary pressure was 17 mm. Hg at rest and rose to 29 mm. Hg during effort.

Tables II III IV and Fig 1 show data derived during catheterization of the coronary sinus. In general changes in heart rate duration of systole and arterial systolic pressure did not differ greatly from those observed during catheterization of the pulmonary artery (Table II). No systematic differences could be found between subjects with sinus rhythm and those with atrial fibrillation. The average pressure time per minute (PTM) was elevated reflecting the fact that 7 patients had intraventricular hypertension and the rise in PTM during stress was 1,230 mm Hg sec./min as compared with 1 020 mm. Hg sec./min in the control subjects. Pressure time per beat rose during exercise from 37.5 to 42.5 mm. Hg sec./beat (+13 per cent)

Myocardial oxygen consumption per 100 Gm. of left ventricle at rest was not significantly different from that in the control subjects (0.5 < p) but a signifi-

*Difference of the change in stroke power between the two groups was not statistically significant.

Table I Systemic hemodynamics during catheterization of the pulmonary artery (congestive heart failure)

	Effective cardiac index (L./min/M²)		Arteriovenous O₂ difference (vol %)		Stroke index (ml/beat/M²)		Systolic ejection rate index (ml./sec/M²)		Stroke power (Gm M./sec./M²)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Mean	2 6	3 7	6 0	9 3	34	35	115	130	205	270
± S D	0 61	1 0	1 3	2 1	10	15	32	45	73	134
Mean	3 4	4 9	4 1	6 3	43	49	160	196	238	332
± S.D	7	1 0	0 8	1 3	10	12	31	44	92	65

*The first two lines apply to the congestive failure series, the last two lines to the control series

Table II Mean values for systemic hemodynamics (congestive heart failure)

	Rest		Exercise	
	Pulmonary*	Coronary†	Pulmonary*	Coronary†
Total body qO_2 (ml./min./M²)	130 ± 19		333 ± 63	
Systemic vascular resistance (dynes sec. cm⁻⁵)	1 315 ± 340		1 245 ± 320	
Left ventricular work index (Kg.M. min./M²)	4 7 ± 2 1	4 7 ± 2 1	7 3 ± 3 0	7 3 ± 3 0
Brachial arterial systolic mean pressure (mm. Hg)	112 ± 27	113 ± 27	131 ± 37	136 ± 31
Heart rate (per min.)	81 ± 14	84 ± 15	111 ± 23	103 ± 18
Systolic ejection period (sec./beat)	0 29 ± 05	0 28 ± 05	0 27 ± 05	[illegible] 27 ± 05

*During catheterization of the pulmonary artery
†During coronary venous catheterization.

-antly greater rise of 5 1 ml /100 Gm of left ventricle per minute was observed on effort (005 < p < 01) in the patients with congestive failure Resting mechanical efficiency index was the same in both groups but since this measurement in patients with congestive failure does not include consideration of regurgitant flow work or the factor of ventricular hypertrophy any such comparison is meaningless In contrast to the findings in the control subjects the mechanical efficiency index did not change during exercise This assumes significance since each patient served as his own control In those patients with aortic insufficiency the unquantified regurgitant volume changes little or actually decreases with exercise * Thus the conclusion that efficiency is unchanged during exercise would appear to be valid

Table III Cardiac performance during coronary venous catheterization (congestive heart failure)

	Brachial arterial systolic mean pressure (mm Hg)		Left ventricular systolic mean pressure (mm Hg)		Heart rate (per min)		Systolic ejection period (sec./beat)		Pressure-time per minute (mm Hg sec)	
	R	E	R	E	R	E	R	E	R	E
Congestive failure series										
Mean	111	136	129	153	84	103	28	27	3 140	4 370
±S D	27	31	27	41	13	18	03	05	1 070	1 370
Control series										
Mean	108	129			82	102	27	26	2 325	3 345
±S D	19	24			15	17	03	02	490	880

*Per 100 grams
R Rest E Exercise

Table IV Dynamics of myocardial oxygen supply

	Coronary arteriovenous O diff rence (vol %)		Coronary venous O saturation (%)				Myocardial O_2 extraction percentage $\frac{A\ VO}{A\ O_2} \times 100$			
			R		E†		R		E†	
	R	E	Pre-exer	Post-exer	3'	7'	Pre-exer	Post exer	3'	7'
Congestive failure series										
Mean	13 0	13 4	24	24	22	22	74	75	76	77
±S D	1 7	1 7	6 5	6	6	7	1 9	2 1	5 5	7 4
Control series										
Mean	13	12	27	29	28	28	72	71	71	70
±S D	1 6	1 7	4 7	7	5 5	5 8	4	6	5 7	6 2

× 10⁴
†3' and 7' = duration of exercise
R: Rest, E: Exercise

In mitral insufficiency, however, regurgitation is primarily a function of the duration of systole per minute, which increased approximately 16 per cent during effort. Thus, in 3 subjects the calculated exercise mechanical efficiency index may have been deceptively low.

The ratio of PTM per oxygen consumption (qO_2) per 100 Gm. of left ventricle was insignificantly higher at rest in the patients with failure than in the control subjects ($0.05 < p < 0.1$). During exercise, oxygen consumption per 100 Gm. of left ventricle rose in direct proportion to PTM. Thus, the ratio between the two did not change significantly ($0.5 < p$), whereas in the patients with normal left ventricles a 17 per cent rise in ratio was observed ($p = .05$). This group difference in the response to exercise is significant.

Pulmonary capillary pressure (mm. Hg)		Left ventricular work index (Kg. M./min./M.²)		Myocardial O₂ consumption (ml./100 Gm./min.)		Myocardial efficiency index (% per 100 Gm.)		Pressure-time O₂ consumption (mm. Hg sec./ml.O₂)	
R	E	R	E	R	E	R	E	R	E
17 9	[illegible] 11	4 7 2 1	7 3 3 0	10 6 2 7	15 7 4 1	23 12	24 10	294 90	286 [illegible]
8 3	10 5	5 0 1 4	8 1 2 1	9 5 2 2	12 0 2 9	24 6 7	35 10 4	246 33	287 63

Coronary flow (ml./100 Gm./min.)		Coronary diastolic vascular resistance (dynes sec. cm.⁻⁵)		Arterial diastolic mean pressure (mm. Hg)		Coronary diastolic filling period (sec./min.)	
R	E	R	E	R	E	R	E
82 21	119 32	60 7 24	42 6 19	77 16	[illegible] 18	36 0 5	32 0 5
82 16	103 21	65 12 7	[illegible] 14	78 11	87 13 5	39 2	31 3 5

(.025 < p < .05). Inasmuch as the resting PTM qO_2 ratio was higher in the subjects with heart failure, a given rise in PTM and qO_2 will produce a smaller change in the above mentioned ratio in the subjects with failure than in the controls. When *absolute* changes in PTM and qO_2/100 Gm. of left ventricle are examined, an increase in PTM of 1,000 mm. Hg sec./min. during exercise costs the normal ventricle 2.4 c.c./100 Gm./min., whereas the failing heart consumes 4.1 c.c./100 Gm./min.

Coronary arteriovenous oxygen difference and oxygen extraction percentage were not statistically different in the two groups at rest (0.05 < p < 0.1). Resting coronary venous oxygen saturation was slightly lower in the subjects with failure (p = .025). When those subjects with failure who had a cardiac index of less than 3.0 L./min./M.² are analyzed separately and compared with the control subjects, the resting coronary arteriovenous oxygen difference was found to be significantly increased (p = .025) and the coronary oxygen extraction percentage greater (.001 < p < .005). During exercise, however, no significant change in oxygen extraction or extraction percentage was observed, as with the control series.

Coronary flow per 100 Gm. was the same as in the control subjects at rest but rose 45 per cent during effort. This rise was significantly greater than in the control subjects (.005 < p < .01) but was due at least in part to the somewhat greater myocardial mechanical stress (PTM) in the former group during exercise. Coronary vascular diastolic resistance per 100 Gm. at rest was similar in the two groups (0.5 < p). With exercise a significant fall in resistance was found (0.01 < p < .025), which was greater in degree than that observed in the control subjects (0.1 < p < 0.2). Coronary diastolic perfusion pressure during exercise rose 15 per cent, whereas the diastolic filling period shortened by 11 per cent.

Analyses of coronary arteriovenous lactate and pyruvate were made in 15 of these subjects at rest and during exercise. The production of excess lactate by the heart* was demonstrated in only 3, with values up to 0.4 mM. per liter of coronary flow. This represented an approximate contribution to myocardial energy metabolism of 0.7 calories per minute or 0.2 c.c. of oxygen per minute.[11]

*Not statistically significant, however.

Discussion

In the analysis of the performance of the stressed failing heart, emphasis has been placed on those aspects of cardiac energetics not usually covered by prior reports, namely, the magnitude and determinants of the energy requirement of the failing heart during physical effort. As in the analysis of the control subjects,[7] the interpretation of observations has been made on the basis of current understanding of cardiac muscle energetics. The major determinant of myocardial energy requirement is considered to be wall tensile force, which in turn is a function of intracavitary pressure and the mean radius of the cardiac chamber.[12-14]

Myocardial performance at rest. In the present study, the oxygen consumption of a unit weight of left ventricle at rest was found to be essentially the same in large hypertrophied hearts as in the normal ventricle. Similar observations by other investigators have been summarized elsewhere.[15] This implies that the degree of myocardial hypertrophy is at that moment commensurate with the increased total energy or oxygen need of the heart and that hypertrophy is appropriate and of sufficient magnitude to enable each unit of myocardium to require only a normal quantity of energy. That the heart should seek to establish a constant energy consumption for each contractile unit is supported by the recent observations of Sandler, Dodge and Hay,[7] who have calculated that the tension developed by each unit of myocardium tends to remain constant in any one heart, regardless of the systolic pressure generated within the ventricle.

In the present report, the average pressure-time per minute of the subjects with congestive failure was 35 per cent higher at rest than that of the control subjects, reflecting intraventricular hypertension in 7 subjects. Despite this fact, the qO_2 per unit weight was not significantly different in the subjects with failure than in the controls. Since myocardial energy need

varies directly with the pressure generated,[11,15] it may be estimated that the muscle mass of the left ventricle in these subjects with failure was increased by approximately 35 per cent because of a chronic *increase in pressure generation alone!*

The oxygen cost per 100 Gm. of left ventricle of pressure-volume work performed by the left ventricle (mechanical efficiency index) was found to be the same at rest in both groups of patients. However, since total left ventricular muscle mass was obviously greatly increased in the subjects with failure, the true efficiency of this pump was certainly subnormal. A more accurate analysis of the efficiency of the failing left ventricle will be made in another report.

Oxygen supply mechanism at rest. The oxygen supply mechanism at rest was not significantly different when the *total* group of subjects with congestive failure was compared with the group of control subjects. However, oxygen extraction and extraction percentage were significantly increased and coronary venous oxygen saturation decreased in those subjects with failure who had subnormal cardiac outputs. Since similar decreases in coronary venous oxygen saturation have been found in other patients with chronically low cardiac outputs (mitral stenosis), this would appear to be a reflection of functionally reduced coronary flow in chronic low-output states rather than anatomic coronary insufficiency secondary to myocardial hypertrophy.[19]

Myocardial performance during exercise. With the stress of exercise, important differences in the energetics of the failing myocardium become apparent. The myocardial stress as evidenced by the change in PTM was slightly greater in the subjects with congestive failure than in the controls. Myocardial qO rose proportional to the increase in PTM (unchanged PTM/qO ratio), whereas in the control group qO_2 rose only 26 per cent while PTM increased 44 per cent. Furthermore, even if the changes in the two groups were similar, an equivalent rise in qO_2 *per unit weight* in the hypertrophied heart implies a greater *total* expenditure of energy than in the heart of normal weight. If there is no change in ventricular volume, a given increment in PTM by the heart should be accompanied by a smaller rise in qO_2 per unit weight *in the hypertrophied ventricle* since a larger muscle mass is sharing the burden of this stress. For example, if two ventricles of equal chamber volume, one weighing 200 grams and the other 100 grams, sustain the same acute rise in PTM, the energy cost of this new effort should be equal in both ventricles. The rise in qO_2 *per unit weight* in the hypertrophied ventricle, however, will be only one half as great as in the thinner ventricle. Earlier it was estimated that the weight of these failing ventricles was increased roughly 35 per cent due to intraventricular hypertension alone. A given increment in PTM therefore should be associated with a rise in qO per unit weight in the failure group of only 74 per cent that of the controls. As shown above, a rise in PTM of 1,000 mm. Hg sec./min. in the control group was associated with a mean rise in qO_2/100 Gm. of 2.4 c.c./min. The expected rise for a similar increment in PTM in the failure group would be 1.8 c.c./min./100 Gm., whereas the observed rise was 4.1 c.c./1,000 mm. Hg sec. Thus, the oxygen cost of generating pressure during effort is greater per unit weight of myocardium in these subjects with failing hearts than in subjects with normal left ventricles despite the increased muscle mass.

A similar defect may be seen on examination of the changes in the mechanical efficiency index in the two groups. A 46 per cent increase in the mechanical efficiency index was observed in the control series during exercise, whereas essentially no change was found in the failure group. A possible explanation of these differences in the response of cardiac efficiency and the amount of pressure generated per milliliter of oxygen may be found in the geometric relationship between tangential wall tension, intracavitary pressure, and the radius of the ventricular chamber. Changes in ventricular volume, independent of the generation of pressure, may alter the energy requirement of the heart chamber. In this manner the rise in PTM/qO ratio and part of the increase in mechanical efficiency observed during effort in the majority of control subjects

can be explained by a decrease in mean radius of the ventricle.[8] In the patients with failure, on the other hand, the energy cost during exercise was larger than normal and directly equaled the increase in PTM. If the hearts of subjects with failure were of the same average weight in relation to chamber size as those of the control subjects, then the finding of an unchanged ratio (PTM/qO_2) would imply that there was no change in mean chamber volume and that rises in pressure followed rises in wall tension. The presence of hypertrophy, however, in relation to chronic pressure load (as exemplified by a higher PTM/qO_2 ratio at rest than normal) indicates that there is a greater muscle mass and total left ventricular qO_2 to develop virtually the same increment in pressure as in the control subjects. Thus, *total* qO_2 probably rose *in excess* of change in pressure, so that one might infer from the unchanged ratio an actual increase in mean chamber volume.* Furthermore, the unchanged stroke volume would indicate that end-diastolic volume had increased as well.

In this connection, the uniform increase in pulmonary capillary pressure (as an index of left ventricular diastolic pressure) is qualitatively helpful in suggesting that end-diastolic volume may have increased. Little information is available, however, concerning ventricular pressure-volume relationships in heart failure. In actual fact, at high filling pressures the ventricle may be on the steep portion of the compliance curve, so that small changes in volume are reflected as large changes in pressure.

It would appear, therefore, that an increase, or at least a lack of decrease, in mean ventricular volume exerts a major influence on the mechanical efficiency of the stressed failing heart. Because of the larger size, tension for any given pressure is greater and, therefore, so is qO_2 or force per unit work[7] in the failing heart. The efficiency of this chamber was further encumbered because fiber shortening distance and rate did not increase and may actually have decreased during effort. This was shown by a fixed systolic ejection rate and stroke volume which were delivered from a presumably larger ventricle. This was in contrast to the rise in mean systolic ejection rate (and fiber shortening rate) of the normal human left ventricle on exercise.

The fixed fiber shortening rate may represent fundamental changes in the structure of the myocardium,[31] but the observed defect is due at least in part to the large initial chamber volume of the failing heart itself. Because the ratio of end-systolic to end-diastolic volume is high in these hearts and the arterial pulse pressure is normal or increased, the ratio of end-systolic to end-diastolic wall tension will be inordinately great.[1,32] Thus, the ability of the myocardial fiber to shorten is further limited by a heightened "after-load," and changes in efficiency are accordingly restricted. Because of these limitations in fiber shortening rate and distance, any production of energy which might be due to the Fenn effect will be accordingly small.

Among other factors which may affect mechanical efficiency is a change in the duration of systole. However, systolic ejection period *per beat* shortened approximately the same extent in both control subjects and those with congestive failure, and the total time spent in systole *per minute* was virtually the same in both groups during stress. Changes in the shape of the ventricle or in the systolic compliance of the chamber during effort are also potentially important considerations, although no such measurements have been made to date. (Parenthetically, it may be noted that any change in compliance due to hypertrophy or fibrosis could act in a favorable fashion to prevent excessive dilatation of the heart when exposed to high filling pressures such as may occur during exercise. The myocardium could function in a manner similar to the pericardium in this regard. Studies by Rolett and associates[33] have shown that acute volume loading *fails* to alter the relationship of PTM to myocardial qO_2 so long as

*Assuming no change in chamber shape, [illegible] constant PTM/qO_2 ratio, the normal heart could have increased its qO_2 4.1 ml./1,000 mm. Hg sec. This implies that in the hypertrophied heart of the subjects with failure (estimated at an average of 35 per cent greater than normal weight) the rise per 100 Gm. is 3.0 ml./1,000 mm. Hg sec. Since the mean rise in qO_2 was 4.1 ml./100 mm. Hg sec., this may signify an actual increase in mean chamber volume during exercise.

the pericardium is intact. Upon its removal however if chamber dilatation occurs, there is a prompt fall in the PTM/qO_2 ratio and mechanical efficiency)

The role played by catecholamines in governing mechanical efficiency of the failing heart is not yet clarified. Chidsey and associates[22] have reported an increase in circulating catecholamines in exercising subjects with heart failure. Raab and coworkers[24] have summarized evidence of the oxygen-wasting effects of catecholamines on the heart. When a synthetic catecholamine is given to normal human subjects or to those with congestive heart failure mechanical efficiency remains unchanged.[8] Occasionally efficiency may increase—a response reported by Welch and associates[21] in dogs with acute congestive heart failure. The latter workers postulated that the reduction in ventricular mean volume (and therefore, force per unit work) caused by catecholamines dominated the energy pattern over other effects of catecholamines. Another curious paradox in the response of subjects with congestive failure to catecholamines concerns the significant increase in mean systolic ejection rate achieved in these subjects after the administration of synthetic catechols[26] a response not seen during physical exercise. Thus it would appear that endogenous catechol stimulation of the heart although perhaps an important factor is inadequate to explain fully the inefficient performance of the exercising failing heart

Myocardial oxygen supply during exercise The virtually unchanged oxygen extraction percentage indicated that the energy needs of the heart during effort were met solely by a greatly increased coronary flow This increase in flow also would serve to show that the increased resting extraction seen in the low-output group was not related to anatomic coronary insufficiency The hydraulic components of coronary perfusion arterial diastolic mean pressure and diastolic time, changed reciprocally and thus, did not contribute significantly to the increased coronary flow In the 6 subjects with aortic stenosis the concept of diastolic vascular *resistance* was valid since no systolic coronary flow occurred through the hypertensive ventricle it is likely that this concept may be applicable in part to the other subjects as well.[1, 29] The fall in this resistance during exercise was significant and of a magnitude similar to that of the controls. Whether this change in resistance is due to vascular or myocardial relaxation is unknown.

Although not statistically significant the greater fall in resistance implies that an equivalent exercise stress called for more coronary vasodilatation in these patients with failure than in the control subjects. The reserve capacity for coronary dilatation was thus further encroached on by poor myocardial performance. During any stress a vicious cycle may develop between inadequate coronary blood flow and inadequate myocardial function.[25] The frequent patchy necrosis and fibrosis of the massively enlarged heart may well come about in this way

Summary

Cardiac performance and myocardial energetics were studied during physical exercise in 19 subjects with congestive heart failure. Mechanical efficiency of the left ventricle was subnormal at rest and failed to rise normally during effort. The oxygen consumed by a unit weight of muscle at rest was not significantly different in the patients with failure than in the control subjects. With physical effort the oxygen consumption rose out of proportion to both the new work performed and the new pressure generated by the left ventricle. Changes in pressure-time/qO_2 ratio suggest that unlike the normal ventricle the failing ventricle is unable to effect a decrease in mean chamber volume during exercise and may actually become larger No consistent evidence for myocardial hypoxia or anaerobiosis during stress was found.

The low mechanical efficiency of the failing heart may be explained by (1) the large chamber volume (and tensile forces required) (2) organic failure or afterload inhibition of change in fiber shortening rate and (3) further increase in heart size on effort The fixed pressure-time per minute per oxygen consumption is *probably* related to an increase in heart size on effort and is a resultant of the above-mentioned factors

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Circulatory effects of chronic pulmonary emphysema

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The concept of "cor pulmonale," created in the distant past as an anatomic and clinical term, has acquired new meaning in recent years when expressed in terms of pulmonary hypertension, right ventricular overload, and right ventricular failure. There are, however, certain areas of controversy, particularly in regard to the cause of pulmonary hypertension and the effect of pulmonary disease on cardiac output. It is noteworthy that most physiologic studies which deal with cor pulmonale have been made on small series of cases, often too small to examine relationship between factors. This study was undertaken in order to assess relationships between various physiologic factors in chronic pulmonary emphysema, the most common cause of cor pulmonale. It was thought that such relationships can best be studied when a large number of cases which represent various stages and severities of the disease are included.

Material and methods

This report deals with 62 hemodynamic studies performed in 59 patients with chronic pulmonary emphysema. The diagnosis was established on clinical grounds and confirmed by ventilatory pulmonary function studies. All patients were treated for bronchopulmonary infections and for cardiac failure, so that hemodynamic studies were performed after each patient reached a plateau of improvement or a stable clinical state. The technical details of cardiac catheterization studies performed in this laboratory have been reported elsewhere;[1] they consisted in this series of measurement of pressures in the pulmonary artery, right ventricle, right atrium, and pulmonary artery wedge position, all recorded during steady state. Determinations of cardiac output were performed in duplicate, using Fick's formula. After these base-line studies were completed, the patient underwent a 3 to 6-minute period of exercise in the recumbent position, during which the oxygen consumption rose to about twice the resting level. Determination of cardiac output and measurements of pulmonary arterial pressure were performed during the final 2 minutes of the exercise period, assumed to represent a steady state. Determinations of arterial oxygen saturation and packed cell volume were made on samples of arterial blood withdrawn during determinations of cardiac output. Results of the measurements and determinations were carefully examined and accepted only when reproducibility of duplicate

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Table I. Data obtained from hemodynamic studies in 59 patients with pulmonary emphysema arranged by decreasing values of arterial oxygen saturation

Patient	Age (yr.)	Mean pressures (mm. Hg): Pulmonary wedge at rest	Mean pressures (mm. Hg): PA Rest	Mean pressures (mm. Hg): PA Exercise	Mean pressures (mm. Hg): RA Rest	O2 consumption (c.c./min.): Rest	O2 consumption (c.c./min.): Exercise	A-V oxygen difference (vol. %): Rest	A-V oxygen difference (vol. %): Exercise	Cardiac index (L./min./M.²): Rest	Cardiac index (L./min./M.²): Exercise	Pulmonary resistance (dynes/sec/cm.⁻⁵): Rest	Arterial oxygen saturation (%): Rest	PCV (%): Rest
H. R.	29	8	23	33		257		5.8	6.1	2.5		305	96.0	51
H. R.	32					291	436	5.1	7.0	3.1	3.5			51
W. Mc.	57		12			270		8.1		3.3			96.0	
R. R.	[illegible]		19	29	7	210	417	5.7	7.7	2.2	3.2		95.1	39
F. W.	63	7	25	43		239	512	7.0	7.2	1.8	3.8	418	94.1	40
N. I.	52	11	15	23	7	225	404	4.9	7.4	2.8	3.3	67	93.0	
H. C.	44	7	20	24		261	507	5.3	7.3	2.9	4.0	207	92.3	47
J. W.	59	6	15	20		236		4.1		3.3		122	92.1	44
J. W.	77	9	18	21	2	261	508	8.6	13.3	1.6	2.1	257	91.5	45
J. L.	72		22	33	2 12	246	615	6.3	10.5	1.9	3.0		91.4	50
L. C.	61				5	207		6.1		2.0			91.0	56.5
A. A.	63	7	22	32	2 10	206	526	5.9	8.3	1.9	3.7	344	90.8	53
B. F.	62	10	30	36	[illegible]	245	458	2.95	5.0	5.0	9.2	160	90.5	[illegible]
M. S.	67	12	26	39		157	313	6.3	8.8	1.7	2.7	442	90.4	48
C. J.	62		25	30		235	402	5.2	7.9	2.9	4.3		90.1	48
R. W.	60	17	20			239	368	3.7	4.1	3.9	4.0	96	90.0	40
R. S.	64	13	45	62		276	636	5.8	12.3	2.6	2.8	532	89.2	58
C. B.	64		18	21		221	407	3.6	5.5	4.0	4.8		89.1	43
B. W.	47	9	21	24		287	612	5.8	7.8	2.8	4.5	193	88.4	42
A. M.	49	8	16	25		312	767	4.8	6.4	3.2	5.7	94	88.3	42
V. P.	60	7	21	26	6	229		4.7		2.9		221	88.3	44
R. B.	46	10	33	42	6-12	224	356	4.3	6.1	2.8	3.4	363	87.9	48
J. B.	64	16	36	48	1	260	482	9.4	15.4	1.5	1.8	375	87.7	53.5
J. G.	67				2	297	522	6.3	7.2	2.5	7.2		87.7	43
J. T.	61	8	15			296		4.0		4.4		76	87.1	60
D. H.	62	7	33			200		4.8		2.4		490	[illegible] 4	41

G. S.	54	4	28	44	8	277	408	3.9	5.9	3.3	3.9	266	87.1	57
G. K.	53	6	23	33	4	148	335	4.7	8.0	3.2	4.2	404	87.0	45
C. G.	51	8	40	70	5	224	479	4.6	8.2	2.7	3.2	320	86.5	51
M. C.	54		30	43		249	585	4.3	6.0	3.0	3.1		86.5	44
E. A.	41	6	29			262		6.8		2.3		592	86.5	62
E. A.	43	8	54	73	5	280	477	4.7	7.2	3.6	4.1	720	86.5	50
A. C.	69	10	40	60	7	[illegible]	411	6.1	8.6	2.3	3.0	650	86.3	57
C. G.	70	5	33	60	10	210	507	5.0	9.7	2.3	2.9	532	86.2	56
J. D.	59	15	26		7	254		5.5		2.9		181	86.2	62
J. D.	59	15	26		7	221		3.3		2.2		207	85.3	61
A. M.	62	3	28	30	6	191	376	4.7	5.0	4.1	5.5	480	85.7	43
M. B.	63		42	45	7	220		5.6	10.0	3.9			85.5	
H. H.	64	8	18	28	3	211	478	3.8	7.4	5.5	6.5	144	85.4	35.5
C. N.	48	6	23	33	14	197		6.1	7.7	2.0		415	85.4	50.2
R. M.	66		14	16	1	127	256	4.9	5.5	2.3	4.7		85.0	33.5
R. M.	57	8	33	45	5	294		5.3		3.3		356	84.5	41
D. J.	63	11	37	47	0–10	237		4.7	7.0	3.1		407	84.2	46
D. B.	42	3	25			232		9		1.9		490	84.0	45.5
E. H.	38	8	28	39	6	232	608	4.6	8.6	2.8	3.8	342	83.7	51
F. J.	36	16	38	38	6–12	256	528	5.2	7.1	3.1	4.6	321	83.4	44
P. P.	65	9	36		3	174		4.3		2.3		555	83.4	
D. B.	41	13	42	60	4	[illegible]	481	4.6	6.5	3.3	4.1	361	83.0	55
G. M.	66		42	50	15	292	371	7.1	14.4	1.9	1.2		82.5	53.5
J. G.	66	6	44	42	2	199	218	5.4	7.3	2.1	1.9	860	82.2	49
F. E.	61	9	43	60	6	283	396	5.4	7.5	3.1	3.1	640	80.5	45
L. M.	62	11	30	50	4	207	473	3.9	6.8	2.9	3.8	310	80.0	44
W. M.	52	13	48	38	8	303	475	5.4	7.7	3.3	3.6	456	80.0	49
F. M.	48		54	65	9	256	496	6.5	12.6	2.2	1.1		79.7	55
L. S.	55	12	30	42	6	177	243	4.9	0	3.6	3.5	207	79.6	57
F. T.	61	6	41	48	6	336	461	6.5	7.8	3.2	3.7	547	78.9	48
A. P.	33		58	76		344	486	6.2	9.4	2.8	2.6		77.0	59
C. H.	33	12	7		4	360		3.6		3.1		200	73.5	66
E. C.	61		35	39	6	222		5.2	7.3	2.2	2.1		72.2	
W. W.	62	11	37			234		4.0		4.0		316	66.2	68
M. R.	57	10	72		5	[illegible]		8.1		2.0		1600	62.0	
C. B.	60	10	50			232		4.6		3.0		640	48.7	66
Mean		9.25	31.7	42.4	5.9	240.7	450.3	5.38	7.92	2.59	3.40	412	83.2	49.76

results was close The measurements considered to be germane to the problem under study underwent statistical analysis for the determination of significant correlations between them

Results

The data collected in this study are presented in Table I The table has been arranged by decreasing values of arterial oxygen saturation In this laboratory oxygen arterial saturation of 92 per cent or less is considered to be abnormally low the studies in 55 out of 62 (88 per cent) patients showed subnormal arterial oxygen saturation If arterial oxygen unsaturation is used as a crude index of severity of pulmonary emphysema it is seen that the series contains mostly patients with a significant degree of pulmonary disease. The mean value for resting pulmonary pressure is at moderate hypertensive level and shows further rise with exercise The range is wide from low normal to severe pulmonary hypertension A similar spread is seen for the calculated pulmonary vascular resistance which shows the mean level at more than twice the upper limit of normal The mean value for resting cardiac output is below the average for normal individuals, although it is still within the normal range. The rise during exercise is 24 per cent above the resting value which is also below average for this laboratory It is noteworthy that the arteriovenous oxygen difference is definitely in the abnormal zone both at rest and during exercise which shows that the cardiac output is shifted toward the normal zone by a higher than average oxygen consumption Other measurements presented in the table show that pulmonary arterial wedge pressure was as a rule a high normal with only two readings above 15 mm Hg Right atrial pressure was definitely elevated in 3 cases thereby indicating right ventricular failure.

A statistical analysis of the relationship between the various parameters is presented in Table II It is seen that a highly significant negative correlation exists between pulmonary arterial pressure and arterial oxygen saturation A less striking but significant correlation is found between the former and the hematocrit reading A barely significant negative correlation exists between calculated pulmonary vascular resistance and arterial oxygen saturation Cardiac output and arteriovenous oxygen difference appear to be totally unrelated to arterial oxygen saturation and packed cell volume However cardiac output shows significant negative correlation with calculated pulmonary vascular resistance.

Discussion

Chronic disease of the respiratory apparatus of which emphysema is the most common affects the right side of the heart and the pulmonary circulation eventually leading to failure of the right ventricle Two mechanisms have been suggested as participating in the overload of the heart pulmonary arterial hypertension and increased cardiac output (high-output state) Pulmonary hypertension is the essential mechanism of cor pulmonale Its cause has been related to arterial anoxemia to reduction of the pulmonary vascular bed and to left ventricular failure.[3] High cardiac output has been thought to be caused by arterial anoxemia and hypervolemia. Its presence in cor pulmonale however is a subject of controversy for some investigators found normal or low cardiac output in this condition

Pulmonary hypertension caused by reactive arteriolar spasm due to anoxemia was first demonstrated by Liljestrand and von Euler[4] in the experimental animal and later confirmed in man[4] The question whether such a reflex maintains itself permanently during chronic states of anoxemia has been widely debated and other causes for pulmonary hypertension have been brought forward in connection with cor pulmonale The results of this study strongly suggest that arterial anoxemia is a principal factor in the production of pulmonary hypertension perhaps the only significant one. Reduction of the pulmonary vascular bed which may be of importance in other forms of pulmonary disease is less likely to play an important role as a cause of pulmonary hypertension in emphysema for it would require an extreme degree of tissue destruction to fall below the threshold for elevation of pulmonary arterial pressure at rest less

than one third of its original size. This mechanism, however, plays a role in causing the accentuation of pulmonary hypertension which occurs during exercise. The factor of left ventricular failure related to arteriosclerotic heart disease is also an unlikely one as a cause of pulmonary hypertension, at least in this series in which almost all patients showed a resting normal left atrial pressure.

The relationship between pulmonary hypertension and arterial anoxemia has to be considered from the broader aspect rather than as an isolated phenomenon which occurs in pulmonary emphysema. It is noteworthy, therefore, that recent studies have established beyond doubt the fact that normal individuals who reside at sufficiently high altitudes to be exposed to chronic anoxia have chronic pulmonary hypertension. Furthermore, chronic hypoventilation due to obesity and other factors produces the same results. The only types of cases in which chronic anoxemia can persist without pulmonary hypertension are certain congenital systemic-pulmonary communications and pulmonary arteriovenous shunts. The most reasonable explanation for this exception is the suggestion by Rossier and Bühlmann that pulmonary hypertension is maintained by intrapulmonary reflexes stimulated by *alveolar* hypoventilation or hypoxia rather than mediated by signals from the arterial side of the circulation.

The concept of "high-output state" in connection with cor pulmonale was introduced by Howarth and associates.[8] The presence of higher than average or higher than normal resting cardiac output during the state of compensation and in failure has been demonstrated in cor pulmonale by some investigators[4] but not by others.[1, 11] It was suggested that increased cardiac output is a compensatory mechanism for anoxemia or that an increase in right ventricular stroke volume secondary to hypervolemia and right atrial hypertension may be responsible for it.[1] Results of this study provide strong evidence against such views: (a) no relationship could be demonstrated between cardiac output or arteriovenous oxygen difference and arterial oxygen saturation nor between the former and hematocrit values; (b) right atrial pressure values were mostly normal and those higher than normal occurred, as a rule, with low cardiac outputs; (c) mean values for the arteriovenous oxygen difference were higher than the accepted normal range; and (d) only one patient of this large series showed abnormally low arteriovenous oxygen differences (B. F.). These observations cast doubt on the occurrence of a high-output state in pulmonary emphysema and particularly on the compensatory relationship between anoxia and high cardiac output. This conclusion finds strong reinforcement in results of recent investigations concerning the effects of anoxemia of high altitude upon cardiac output. Neither short term exposure to high altitude nor chronic residence at anoxic levels causes an increase in cardiac output.[9, 14] In view of these considerations, a review

Table II. Statistical evaluation of the data presented in Table I

	N	t	p
1. Pulmonary arterial pressure vs. arterial oxygen saturation	60	−7 28	< 00001
2. Pulmonary arterial pressure vs. packed cell volume	57	3 15	0026
3. Pulmonary vascular resistance vs. arterial oxygen saturation	46	−2 01	05
4. Cardiac output vs. arterial oxygen saturation	62	−0 586	56
5. Arteriovenous oxygen difference vs. arterial oxygen saturation	62	0 676	502
6. Cardiac output vs. packed cell volume	56	−0 48	62
7. Cardiac output vs. pulmonary vascular resistance	46	−3 6	0006

N: Size of sample.

Sampling distribution: $\sqrt{\frac{N-2}{1-r^2}}$

p: Probability of the sample correlation of independent bivariate normal variates exceeding the observed values of

Table III. Collected data concerning mean values for cardiac index and arteriovenous oxygen difference in series of cases of cor pulmonale

Author	*Number of cases*	*Cardiac index (L./min./sq. M.)*	*Arteriovenous oxygen difference (vol. %)*
Hickam and Cargill[18]	5	3.9	4.4
Borden, et al	24	3.1	4.7
Harvey, et al[19]	29	3.6	4.2
Lewis, et al	16	3.9	4.4
Fowler, et al[12]	15	2.7	4.9
Yu, et al[10]	18	3.6	4.3
Mounsey, et al[17]	24	4.4	4.3

of the observations which led to the development of the concept of a high-output state in cor pulmonale was undertaken.[10-15, 18] Table III presents mean values for the arteriovenous oxygen difference and the cardiac index in various series dealing with cor pulmonale. It is seen that in none of the group of cases has the mean arteriovenous oxygen difference exceeded the lower limits of normal of 3.5 volumes per cent. Inasmuch as arteriovenous oxygen difference may be a more reliable index of circulatory adequacy than is cardiac output,[20] the concept of "high-output state" in connection with cor pulmonale appears in doubt. Arguments that normal cardiac output in the presence of heart failure is equivalent to a "hypercirculatory state" are also of questionable validity, for normal cardiac output can be found in an appreciable number of patients with hypertensive and ischemic forms of heart failure.[21] The most acceptable is the suggestion of Mounsey and associates[7] that the higher than average cardiac output found in cor pulmonale is due primarily to higher oxygen consumption caused by increased respiratory effort.

Studies on pulmonary hypertension other than cor pulmonale have brought out the observations that high pulmonary arterial pressure is usually associated with low cardiac output, and it is assumed that high pulmonary vascular resistance exerts a restrictive influence upon the flow through the lungs. This concept finds confirmation in this study by the negative correlation between cardiac output and pulmonary vascular resistance.

Findings of this study present convincing evidence that pulmonary hypertension in cor pulmonale is related to anoxemia. On the other hand, no evidence has been found in this study, nor by observations in high altitude, for a hyperkinetic circulatory state. The difference between cor pulmonale with heart failure and other forms of heart failure—if there is any—may be related to two factors usually present in pulmonary disease: (a) increased respiratory effort and (b) frequency of bronchopulmonary infections, both of which may significantly increase the demands upon the circulation. The problem of the recovery from cardiac failure in cor pulmonale has not been consistently investigated. Observations by Harvey and associates[8] and Ferrer and associates[9] that cardiac output is higher in patients who are in failure than in those out of failure are based on a small number of cases and have not been confirmed by other investigators.

Summary and conclusions

A series of 59 patients with moderately severe and severe pulmonary emphysema was studied by subjecting them to hemodynamic examination at rest and during a standardized exercise test at the time when they were in a clinically stable state, i.e., at the point of optimal response to cardiac therapy and free from bronchial infection. These patients represented a broad spectrum of disturbances of respiratory function; with resting arterial oxygen saturation used as a crude index of adequacy of pulmonary gas exchange, they ranged from normal to grossly disturbed in function. Findings of the study, particularly pulmonary arterial pressures, pulmonary vascular resistance, cardiac output, and arterial oxygen saturation, were subjected to a statistical analysis for the purpose of determining relationships between the various parameters.

A significant negative correlation was found between arterial oxygen saturation and pulmonary arterial pressure. This was interpreted as evidence that pulmonary

hypertension the essence of cor pulmonale due to pulmonary emphysema is related to and could be caused by chronic anoxemia in a manner similar to pulmonary hypertension of high altitude No relationship could be demonstrated between cardiac output or arteriovenous oxygen difference on the one hand and arterial oxygen saturation on the other hand This was considered to be a strong argument against the concept of the occurrence of a compensatory high-output state in anoxemia. A critical survey of previous work failed to show satisfactory evidence that a hypercirculatory state exists in cor pulmonale due to emphysema. The occasional occurrence of high cardiac output in cor pulmonale can be satisfactorily explained by elevated oxygen consumption due to increased respiratory effort and bronchial infection.

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Cardiac changes in myopathy

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Although cardiac involvement in myopathic disorders is well known, the published reports consisted of isolated case reports or short series[1-6] until Rubin and Buchberg[7] and Weisenfeld and Messinger[8] focused attention on this association and suggested that cardiac involvement may be present in 50 to 85 per cent of the cases of muscular dystrophy.

Recently, Manning and Cropp[9] have reported electrocardiographic findings in 28 cases of pseudohypertrophic muscular dystrophy and 10 cases of facioscapulohumeral myopathy. In 25 cases of the pseudohypertrophic group the electrocardiograms were abnormal, in 2 others the findings were questionable (possibly normal), and in only 1 was the graph normal in all respects. These authors thought that deep Q waves in the left ventricular leads and tall R waves in Leads V_1 and V_2 were seen so often (70 to 75 per cent) that they could be considered to be a specific feature of this form of myopathy, particularly when no such changes were seen in the facioscapulohumeral group.

This report records our observations on 70 cases of various forms of myopathies studied between 1956 and 1960.

Methods and material

All these patients had a thorough neurological and cardiovascular checkup clinically. A skiagram or radioscopic findings and a 12-lead electrocardiogram were available in every case. One patient in whom the clinical findings were suggestive of atrial septal defect was catheterized for us by Dr. Padma Vati and the late Dr. Devi Chand at Delhi.

Patients coming for a follow-up underwent repeated clinical, radiologic, and electrocardiographic investigations. In atypical cases, muscle biopsy was performed in order to confirm the diagnosis of myopathy.

Observations

These 70 cases could be subdivided according to their clinical pattern as follows: pseudohypertrophic group, 60 cases; scapulohumeral, 6 cases; unclassified, 2 cases; myasthenic myopathy, 1 case; and thyrotoxic myopathy, 1 case. For further observations, only the first two groups are considered. No clinical or electrocardiographic abnormality was seen in the other 4 cases.

Pseudohypertrophic muscular dystrophy group. The average age of the patients at the time of first observation was 15.3 years, with a range of 5 to 39 years. With regard to age, they could be divided into the following groups: under 10 years, 25 cases (41.66 per cent); 10 to 19 years, 28 cases (46.66 per cent); 20 to 29 years, 6 cases (10.01 per cent); 30 to 39 years, 1 case (1.66 per cent).

There were 4 girls (6.61 per cent) in this series. In about 19 cases there was a history

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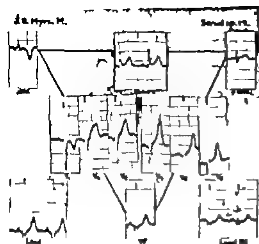


Fig 1 Show prominent R pattern. Note the presence of prominent R with counterclockwise rotation at the same time.

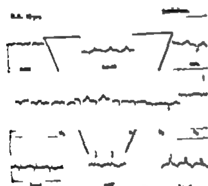


Fig 2 Show prominent R and deep Q wave in Leads V1, I and V5-V. Note flat T waves in Leads V5-V

of similar muscular disorder in more than one member of the family

Two patients showed evidence of congenital cardiac anomalies one had ventricular septal defect (clinical diagnosis) and the other had atrial septal defect or anomalous pulmonary venous drainage (determined by cardiac catheterization) Another 25-year-old patient was hospitalized with congestive cardiac failure and died within 36 hours of admission. His case record and autopsy data are presented separately (*vid infra*) Except for these 3 none of the patients had evidence of clinical heart disease.

Radiologic investigations also failed to reveal any gross abnormality in cardiac size or configuration except in the 2 patients with congenital cardiac lesions. Changes similar to cystic bronchiectasis were seen on straight skiagram of the chest in 2 patients, but no bronchographic proof was available. However similar cases of bronchiectasis proved by bronchography were reported by us earlier [11] Three patients had associated hypogonadism (one case proved by autopsy and the other 2 by testicular biopsy) One of these 3 patients had marked obesity resembling Fröhlich's syndrome.

In contrast with the relative paucity of clinical and radiologic abnormalities, the electrocardiographic changes were conspicuous.

ELECTROCARDIOGRAPHIC CHANGES These changes in a smaller series have been reported in detail elsewhere [12] and only important changes are presented below

The average cardiac rate was 98 6 per minute with a little more than half the patients showing sinus tachycardia No significant change in cardiac rhythm was noted except occasional ventricular extrasystoles in 2 patients.

The P wave was normal in shape height and duration in most of the patients

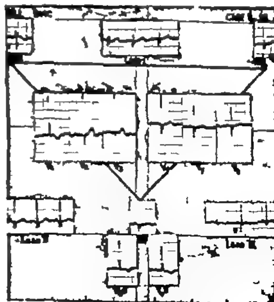


Fig 3 The ECG shows typical myopathic pattern—short P R interval, prominent R deep Q wave in Leads V5-V and V1, splintered QRS complex, and poor voltage T wave in Leads V and V6.

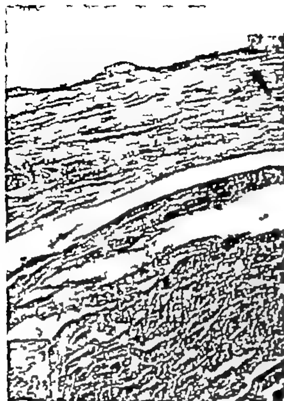


Fig. 4 Section of heart muscle, showing swollen muscle fiber with indistinct nuclei giving a dirty white appearance. (Hematoxylin and eosin × 80.)

The P-R interval was measured in Leads II and V_1 and the average figures were 0.13 and 0.12 second, respectively. Over two thirds of the patients showed a P-R interval of 0.12 second or less.

The QRS interval was within the normal range. In 21 patients (35 per cent) $S_{V1} + R_{V5}$ was more than 35 mm. and the maximum was 70 mm. As a rule, all these patients had a large R_{V5} (25 mm. or more). In 14 patients (23.3 per cent) $S_V + R_{V5}$ was more than 40 mm.

As a rule, the patients showed a prominent R wave in Leads V_1 and V_2. Taking an R/S ratio of 1.5 to be the top normal for this age group,[11] we found that in three fourths of the patients the R/S was over 1.5 in Lead V_1. This could be taken as evidence of right ventricular hypertrophy, but it is important to point out that most of these patients showed counterclockwise rotation and about one half of them had prominent R_V suggestive of left ventricular hypertrophy (Fig. 1).

Thirty-six patients (60 per cent) showed a deep Q wave in Leads V_5, V_6 and aV_L or aV_F, depending upon the cardiac position. There were 11 patients who showed a deeper Q wave in Lead aV_L, whereas the Q wave in Leads V_5-V_6 was normal (Figs. 2 and 3).

Seven patients (11.6 per cent) showed an rSR pattern in Lead V_1, but no patient had frank evidence of bundle branch block. These 7 patients showed splintering of the QRS complex in other leads as well.

The RST segment was isoelectric and normal in shape in most of the patients.

About 20 per cent of the patients showed T waves which were of poor amplitude, flat, or inverted in the left ventricular surface leads.

Q-T was measured in all patients in either Lead V or Lead V when T and U waves could be clearly defined. The average Q-T was 1.05, with a range of 0.90 to 1.15. About 82 per cent of the patients showed a Q-T of 1.01 or over, and 16 patients (26.6 per cent) had a Q-T of more than 1.08. This suggests that Q-T



Fig. 5 Section of heart muscle, shows a high-power view of the changes seen in cardiomyopathy. (Hematoxylin and eosin ×160.)



Fig. 6. Section of skeletal muscle, shows swollen appearance with partial loss of striations and early fragmentation. (Hematoxylin and eosin ×160.)

had a tendency to be prolonged and about one fourth of the patients showed a definitely abnormal Q-T$_c$.

In 42 patients (70 per cent) the electrocardiographic findings could be interpreted as being suggestive of myocardial damage according to the known accepted criteria. Mostly such abnormal patterns were various combinations of the changes discussed above.

Presented below are the autopsy data of a case.

CASE REPORT. M. S., a 25-year-old man, was hospitalized with frank signs of congestive heart failure. The blood pressure was 115/70 mm. Hg. Femorals +. Cyanosis +. The heart was obviously enlarged. Cardiac auscultation was noncontributory. The patient showed a pattern of pseudohypertrophic myopathy in atrophic stage. He seemed to be very ill and died within 36 hours of admission to the hospital. No radiologic or electrocardiographic investigation could be made. The autopsy findings were as follows.

The body was moderately built and nourished. The face was puffy. The fingers showed cyanosis. Pitting edema was present on the sacral region. Examination of the heart revealed moderate enlargement. It weighed 380 grams. No fluid was present in the pericardial cavity. The walls of all the chambers of the heart were thinned out, the right ventricular and left ventricular walls measured 0.3-0.4 cm. and 0.4-1.4 cm. respectively. All the cardiac chambers were dilated but the valves appeared to be normal. The aorta showed atheromatous plaques. The other viscera showed congestive changes. The skeletal muscles appeared to be more or less normal in color and consistency.

On microscopic examination the pericardium was normal but myocardial bundles were swollen and edematous. An opaque, dirty material was seen in some of the muscle fibers which had indistinct nuclei and partial loss of striations (Figs. 4 and 5). In other areas the muscle fibers were shrunken, and fatty infiltration was present. Sections of the skeletal muscles showed varying degrees of degeneration, with loss of striations and fragmentation (Fig. 6). There was marked evidence of sarcolemmic reaction, with proliferation and invasion of the sarcoplasm forming clusters (Fig. 7). Some muscle bundles showed great swelling and deposition of dirty material in the sarcoplasm. The muscle bundles were separated and showed fatty change and perivascular lymphorrages in some areas (Fig. 8).

The autopsy data showed findings of cardiopathy and congestive failure in association with muscular dystrophy. The lungs showed congestion and terminal pneumonia.



Fig. 7. Section of skeletal muscle shows marked sarcolemmic reaction and subsequent atrophy of the muscle fibers. (Hematoxylin and eosin ×60.)



Fig. 8. Section of the skeletal muscle, showing swelling and opacity of the sarcoplasm. The muscle bundles are widely separated by fibro-fatty tissue showing round cell infiltration. (Hematoxylin and eosin ×160.)

Facioscapulohumeral group. There were 6 cases in this group. All were males and they ranged in age between 17 and 38 years (average age of 24.5 years). Except for 1 patient who showed evidence of mitral stenosis and aortic stenosis and regurgitation presumably rheumatic in origin in view of a positive history of rheumatic fever, none had any clinical cardiovascular abnormality. This single exception had radiologic changes consistent with the aforesaid valvular lesion. The others had normal cardiac silhouettes.

ELECTROCARDIOGRAPHIC FINDINGS: Cardiac rate varied from 60 to 100 per minute and the average was 81.3 per minute. No abnormality of rhythm or voltage was seen. The P wave was normal in shape, height, and duration, except in the patient with mitral stenosis who had P mitrale. The P-R and QRS intervals and Q-T were normal. Except in the patient with the valvular lesion, the S_{V} + R_{V} and R/S_{V1} were within the normal range. No slurring of the QRS complex was noted. The RST segment and T waves were normal in shape and amplitude.

In short, except for the patient with obvious cardiac lesion, the electrocardiographic records were significantly normal.

Discussion

Cardiac involvement in myopathy may present as (1) congestive cardiac failure, (2) persistent tachycardia and/or arrhythmias, (3) or electrocardiographic findings in the absence of any evidence of clinical heart disease. These remarks apply only to the pseudohypertrophic muscular dystrophy group, since the facioscapulohumeral group seems to be free of any of these stigmata. This has been reported by Manning and Cropp[10] and our findings amply confirm this.

Congestive cardiac failure is relatively uncommon in muscular dystrophy, probably because the wasting of skeletal muscles limits the activity of the patient. In our study, there was only one patient who had evident congestive failure and died within 3 days of admission to the hospital. It is also possible that the involvement of cardiac muscle is not so extensive and severe as to precipitate congestive failure although sufficiently widespread to modify the electrocardiographic pattern. This has been the experience of previous workers[7, 10] and our data confirm this. The pathologic lesions in the cardiac musculature of the only patient who had congestive cardiac failure gives additional support to this hypothesis. Similar widespread changes in the cardiac muscle have been reported before,[4, 17] but it cannot be claimed that these changes are characteristic of cardiopathy associated with muscular dystrophy.

In view of our findings and the previous literature it seems that electrocardiographic changes are probably the earliest manifestation of cardiac involvement in muscular dystrophy, but we would like to review this opinion after the data are completed on vectorcardiographic changes, cardiodynamics, and serum enzyme studies which are being done at the moment.

Although Rubin and Buchberg[7] found some cases with abnormal graphs and Weisenfeld and Messinger[4] emphasized

this association. Manning and Cropp[8] were the first to suggest that certain electrocardiographic changes are specific of cardiac involvement in muscular dystrophy. However, Keith and associates thought it unwise to attach too great a significance to such minor changes as they noted in a smaller series. We have previously reported[12] findings similar to those of Manning and Cropp[8] and confirm the same with a larger series. We feel tempted to suggest that the following electrocardiographic changes are seen so frequently and consistently that it will not be wrong to use the term "myopathic pattern": sinus tachycardia, short P-R interval, R/S_{V_1} more than 1.5, deep Q wave in Leads V_4, V_5, V and other left ventricular leads, especially Lead aV_L.

Besides these findings, the prominent R_{V_1} with T waves which are of poor amplitude, flat, or inverted in left ventricular leads and splintering of the QRS complex are findings that are often associated.

It is difficult to explain these changes satisfactorily. Manning and Cropp[8] suggested that this pattern is due to such disturbances of the initial QRS vector as a result of myocardial damage that it takes the form of the infantile vector loop which is abnormal for this particular age group in view of the accepted standards. However, this hypothesis needs corroboration from vectorcardiographic studies.

Recently Gailani, Danowski, and Fisher[13] reported hemodynamic data obtained by catheterization of the right side of the heart in 12 patients with muscular dystrophy. Their findings suggested that some of these patients may be having latent congestive failure. They believed that the electrocardiographic pattern was not due to pulmonary hypertension or right ventricular hypertrophy but may have been a variant of conduction disturbance. These are interesting findings which need confirmation.

Lastly, we fail to explain why only cases of pseudohypertrophic muscular dystrophy show this peculiar myopathic pattern whereas cases of allied facioscapulohumeral myopathy are entirely free—although this difference in the electrocardiographic pattern may be used as an aid in differential diagnosis.

Summary

Clinical, radiologic, and electrocardiographic data from 70 cases of myopathic disorders are presented. In one case cardiac catheterization was performed and in another complete autopsy. The electrocardiographic changes were limited to the pseudohypertrophic muscular dystrophy group, whereas the facioscapulohumeral group and those with other myopathies were completely free of such stigmata. An electrocardiographic combination of sinus tachycardia, short P-R interval, R/S_{V_1} more than 1.5, deep Q wave in Leads V_4, V_5, V and aV_L, and prominent $R_{V_1-V_2}$ was seen so frequently that the term "myopathic pattern" could be used for it. The autopsy-proved case (patient who had frank congestive failure) showed extensive involvement of the cardiac musculature similar to that of the skeletal muscles and thus confirmed the association of cardiopathy in myopathic patients. Satisfactory explanation for these changes demands further investigations, such as vectorcardiography and cardiodynamic studies. No explanation is available why patients with other myopathies do not show similar electrocardiographic changes.

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Acyanotic ventricular septal defect with both great vessels from the right ventricle

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In this malformation the pulmonary artery arises normally from the outflow tract of the right ventricle but the aorta arises abnormally from the inflow tract or sinus portion of the right ventricle. When the ventricular septal defect lies below the aortic valve, the remarkable streaming of left ventricular blood through the defect and out the aorta is such that in the absence of severe resistance to pulmonary blood flow the patient is not visibly cyanotic. Under these circumstances, the history, physical findings, and most laboratory studies closely resemble the features of a simple ventricular septal defect with pulmonary hypertension.[1-4] The surgical implications of these two types of ventricular septal defect are vastly different, however.[4,6] The problems posed in diagnosis and management are illustrated by the first 2 patients encountered with this malformation in 1959.

Illustrative cases

J. H. and Je. V. were born in October, 1956. Because of heavy breathing and poor gain in weight they were brought to The New York Hospital at the ages of 6 and 8 weeks, respectively. Both had bulging, overactive precordium, with holosystolic thrill and murmur maximal along the lower left sternal border. S_2 on the left was accentuated. Respiratory distress and hepatic enlargement were present. Pulse pressure was normal. There was no cyanosis.

X-ray films showed enlargement of all four chambers, and a prominently convex main pulmonary artery with engorged pulmonary vasculature (Fig. 1,*A*). In the left anterior-oblique projection the appearance of the ascending aorta was not unusual (Fig. 1,*B*).

Electrocardiograms demonstrated conduction disturbance over the right ventricle and combined right and left ventricular hypertrophy as well as left ventricular "strain." The electrical axis was 90° in J. H. and 30° in Je. V.

The diagnosis in each was ventricular septal defect with greatly increased pulmonary blood flow and pulmonary hypertension, in congestive heart failure. Except for the disappearance of the signs of heart failure under treatment, their cardiac findings remained unchanged as they grew. They underwent cardiac catheterization, in anticipation of surgery, at the ages of 2½ months. The data are summarized later in Table V (see J. H. and Je. V.). Both showed a left-to-right shunt at the ventricular level. Neither the normal arterial oxyhemoglobin saturation of 97.2 per cent (J. H.) and 96.7 per cent (Je. V.) nor the dye-dilution curves gave evidence of a right-to-left shunt. Both had pulmonary hypertension. Pressures in a systemic artery were not measured simultaneously with pressures in the right heart. Because of a question of branch stenosis of the pulmonary artery in Je. V., intravenous

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Fig. *1.* Case 1, J. H. *A*, Frontal roentgenogram showing convex main pulmonary artery in its usual position. Cardiomegaly and increased pulmonary vasculature. *B*, Left anterior-oblique projection. Position of the aorta appears to be normal.

angiocardiograph performed. No stenosis was seen, and the sequence of opacification of cardiac chambers and great vessels was normal (Fig. 2).

Open-heart surgery to repair the defect was undertaken in April, 1959, for J. H. and 6 months later for J. V. Through a right ventriculotomy the edges of the defect were sutured together. Neither patient survived.

Even at postmortem examination the true nature of the malformation was not revealed until the left ventricle was opened. Then it was seen that the ventricular septal defect had been the only outlet for the left ventricle and that the aortic valve was located in the sinus portion of the right ventricle posteromedial to the pulmonary artery.

Comment. Review of the findings in search of a clue that would permit diagnosis before operation and prevent such an outcome led us to think that patients with a ventricular septal defect and a right ventricular pressure at or near a systemic level should be suspected of having aortic transposition even though they were acyanotic. The right ventricular pressure in these two girls would probably have been as high as the systemic pressure if the two pressures had been measured simultaneously. Demonstration of the abnormal aortic origin might then be made by contrast studies in the left anterior oblique projection, when the transposed aortic valve should appear anterior to the plane of the ventricular septum above the right ventricle.

When the intravenous angiocardiograms of Je. V. were then re-examined, we saw what we had not noticed previously: that although the aorta filled only at the appropriate time after left ventricular opacification and appeared to be normal in the frontal projection, yet in the lateral view the aortic valve could be seen anterior to the plane of the ventricular septum, arising from the right ventricle (Fig. 2).

It was evident that we needed to understand the malformation better so that we could make the correct diagnosis and devise an operation that would interrupt the interventricular shunt and at the same time permit left ventricular blood to tunnel unobstructed into the aorta.[1]

Postmortem review

First, we reviewed the postmortem specimens of ventricular septal defect which had been saved over the preceding 10 years, and we found 10 examples of this malformation, none of which had been recognized prior to this search. The chief causes for failure to note the transposed aortic origin at autopsy were two. First, on the right ventricular side, was failure to bivalve the ventricle sufficiently to see its inflow and outflow tracts and where the septal defect led. Second, on the left ventricular side, was failure to deflect sufficiently or to cut through the aortic leaflet of the mitral valve to see the aortic valve and to verify its origin. Simply to pass a probe from a ventricle into the aorta was not adequate to tell the relationship to the septum and ventricles.

The ages at death of the autopsied patients are listed in Table I and are quite like those for patients with ventricular septal defect in general. Some patients did not survive to be born alive at term. Others died in heart failure in the first months of life. The only deaths after age 7 months were surgical: the 2 patients whose cases were just cited and a third who died in 1962. In the third, W. C., the correct diagnosis was made during life and a hammock prosthesis was used at operation. However, he had coexistent aortic insufficiency and had been in heart failure. He did not survive the attempt to correct the defect and the regurgitant aortic valve.

Next, we began to review and restudy by various angiocardiographic techniques those living patients with ventricular septal defect who had a systemic pressure in the right ventricle. In this manner we made the diagnosis in 8 other patients. In 2 of these the diagnosis was confirmed at operation and in 1 of them at autopsy as well. The 3 oldest patients were first seen at the ages of 6, 7, and 14 years, and 2 of them have been under medical observation for 13 years each. The present ages of the living patients are given in Table II. This distribution is also like that for simple ventricular septal defect with normal aortic origin.

Except for the results of angiocardiography, the findings in these patients were indistinguishable from those in patients who had the usual ventricular septal defect with high right ventricular pressure and a left-to-right shunt. On physical examination the thrill and murmur were those of the septal defect. The accentuated and narrowly split S_2 in the second left intercostal space would be expected when the pulmonary artery is in normal position and there is pulmonary hypertension. This sign would not ordinarily be interpreted then as suggesting dextroposition or transposition of the aorta. None of the patients were visibly cyanotic. Conventional roentgenograms and fluoroscopy showed that the convex pulmonary artery was in normal position and gave no clue in the left anterior-oblique position to the abnormal origin of the aorta (Fig. 1).

Nor were the electrocardiograms of value in differential diagnosis. The interpretation of the multiple unipolar precordial leads is given in Table III for 15 of the 16 patients on whom records were taken. The number of patients with each combination of abnormalities is shown in the last column on the right. The number showing each abnormality is tabulated at the bottom. It may be significant that there was no patient with isolated left ventricular hypertrophy. It is curious but true that 1 patient had no abnormality in the precordial leads. She was 14 years old when the first record was made, and there was no change 5 years later. With this single exception, all patients showed right ventricular hypertrophy. This is in keeping with a systemic pressure in the right ventricle but does not suggest the abnormal aortic origin.

Neufeld's report of cases suggested that an electrical axis around $-90°$ was characteristic of this malformation, but our experience indicates that the electrical axis is quite variable and not of diagnostic value. (See Table IV.)

The findings at cardiac catheterization are summarized in Table V. They too



Fig. . Case 2, Je. V. Angiocardiogram. The aorta filled only after opacification of the left atrium and ventricle. The aortic valves and ascending aorta are anterior to the plane of the ventricular septum and above the reopacified right ventricle.

Table I Age at death 13 patients

Age		Number
Medical		10
Stillborn premature	3	
1 wk	3	
2 3 mo	3	
7 mo	1	
Surgical		3
2 3 yr	2	
11 y	1	

Table II Present age of 8 living patients

Age	Number
Under 2 y	1
2 5 y	3
10 15 y	1
16-20 y	3

Table III ECG abnormalities 15 of 16 patients

IRBBB +	RVH +	LVH +	LVS	Number of patients
+	+	+	+	5
+	+	+		1
+	+			3
	+	+	+	1
	+	+		3
	+			2
		+		0
9	15	8	6	Number of patients

Table IV Electrical axis 15 patients

−90°	3
L	0
N	4
+90°	7
R	2

failed to differentiate normal from transposed aortic origin for in all but 1 patient the oxyhemoglobin saturation in the systemic circulation was normal or very nearly so. Exercise did cause a drop in saturation in D B and may have been responsible for the unsaturation in A F an infant who was crying when this determination was made and who had not previously or subsequently appeared blue Her intravenous angiocardiogram did not show premature opacification of the aorta (see Fig 5 below)

Noteworthy is the variation in systolic pressures in the right ventricle and a systemic artery when they were not measured at the same time Differences of about 20 mm Hg were seen In the patients in whom the recordings were simultaneous and were repeated during the procedure variations in systolic pressure of the same magnitude were observed but each time the systolic pressures in the right ventricle and a systemic vessel varied together and were the same.

Like patients with simple ventricular septal defect these patients with increased pulmonary blood flow may have some pulmonary stenosis, yet a higher than normal pulmonary artery pressure One patient (W C) with greatly increased pulmonary blood flow had a relative pulmonary stenosis with a large infundibular pressure gradient yet a slight pulmonary hypertension Another (J F) had the same systolic pressure in the pulmonary artery as in the right ventricle at the time of her first cardiac catheterization at another hospital when she was 7 years old but 3 years later she had acquired some infundibular obstruction indicated by a pressure gradient of 20 mm Hg With severe pulmonary stenosis and hypotension in the pulmonary artery and with decreased pulmonary blood flow this malformation with transposed aorta mimics and must be differentiated from tetralogy of Fallot with varying degrees of overriding aorta [4,8]

Table V indicates the ratio of pulmonary-to-systemic blood flow usually in the range of 1.5 or 2 to 1 Pulmonary vascular resistance was elevated to some extent in all patients. Dye-dilution curves indicated in some a small right to-left shunt. The degree of shunting at any one moment depends on the efficiency with which left ventricular blood tunnels into the aorta as well as on relative resistance to flow in the two circulations. Accessory guides are especially important in evaluating the pulmonary blood flow physical findings of

an enlarged and overactive heart fluoroscopy and roentgenograms for pulmonary vascular pattern and pulsations, and evidence on the electrocardiogram of left ventricular overwork

The presence of congestive heart failure early in infancy is another sign of excessive pulmonary blood flow at that age Ten patients were observed to be in heart failure in their first 6 months of life and were treated for that complication 5 of these died in heart failure. Three others who survived infancy probably were in heart failure then for they gave a history of "pneumonia" that was recurrent A fourth patient who gained practically no weight in the first year and was fed by medicine dropper for months was probably in heart failure also. These observations would indicate that 14 of the 18 patients born alive had a sufficiently low pulmonary vascular resistance in infancy to accommodate an excessive pulmonary blood flow

In contrast is 1 infant, A F who has been under observation from the age of 4 months, and who has never manifested any of the features of excessive pulmonary blood flow She would appear to have retained a fetal type of pulmonary vascular bed with a resistance high enough to limit pulmonary blood flow to an average amount

Although cardiac catheterization n these patients did not make the diagnosis of transposed aorta with the ventricular septal defect it did select the group for further studies with contrast medium in the left anterior-oblique (or left lateral) projection[9] those with a pressure in the right ventricle at or near systemic levels

Contrast visualization

Fig 3 shows the roentgenogram of the chest of the oldest patient (Jo. V) The prominence of the main pulmonary artery in its usual position is evident. Intravenous angiocardiography confirmed the normal position of the pulmonary artery and showed normal sequence of opacification of chambers and vessels.

Fig 4 which shows the selective left ventricular injection, was obtained when the tip of the catheter slipped through the defect and into the left ventricle. The frontal projection (*A*) gave no hint of the abnormal position of the aortic valve but in the left anterior-oblique projection (*B*) the plane of the ventricular septum was clearly seen. The aortic valve was not in its normal position above the left ventricle Instead the contrast medium flowed through the ventricular septal defect and into the transposed aortic valve, located in the right ventricle, entirely anterior to the plane of the septum Some contrast medium also entered the right ventricle

Fig 5,*A* is the intravenous angiocardio-

Table V

Patient	*Age*	*Sex*	*Pressures (mm. Hg)*			*PBF/SBF*	*Systemic oxygen saturation* (%)
			RV	*PA*	*SA*		
A O.	17	F	85/1	86/42	82/60	2 6	[illegible]
D B	14	F	114/7	113/62	118/78	1 1	95 7
Jo.V	11	F	120/0	80/30	120/80	1 5	91 9
J F	10	F	97/3	57/34	97/61	1 6	93 1
	7		74–85/7	71/42	94/34	1 5	87
W C.	9	M	110/5	29/14	111/31	2 5	92 5
G H.	3	M	105/2	105/50	103/63	1 2	90 6
	3 mo.		89/3	—	—	3 0	95 7
J.H	2	F	65/1	66/26	88/46	4 4	97 2
Je.V	2	F	70/2	70/15	—	1 9	96 7
J C.	2	M	69/1	66/30	84/40	2 1	92 4
A.F	10 mo	F	96/5	96/48	80–100/60–80*	1 0	81 5
A B.	7 mo	M	73–84/3	100/32	100/60	1 8	97 2

Cuff



Fig 3 Roentgenogram of Jo. V showing marked con ex main pulmonary artery in its usual location and increased pulmonary ascular markings.





Fig 4 Selecti left entricular injection in Jo. V *A* Frontal view show the aorta filling from the left entricle nd does not suggest bnormal posi tion of the aortic alve. *B* Left anterior-oblique iew shows contrast medium flowing through the entricular septal defect and into the aorta hich is entirely anterior to the plane of the entricular septum. Some material spills int the right ventricle (Picture by courtesy of Dr Leonard Steinfeld, Mt Sinai Hospital New York N Y).

gram of one of the youngest patients (A F) who was studied at 10 months of age As in most of the other angiocardiograms of these patients, only the pulmonary artery opacified at the time of right ventricular filling and the aorta filled after the left ventricle This is another example of the extraordinary separation of flows in this form of double-outlet right ventricle.

B and *C* of Fig 5 illustrate the selective right ventricular angiocardiogram on this same patient By good fortune, the tip of the catheter in the right ventricle lay just beneath the aortic valve so that the earliest opacification at the time of injection was of the transposed aorta (*B*) When the contrast material spread through the right ventricle, it then entered the pulmonary artery and returned to the left ventricle by the normal route (*C*) The plane of the ventricular septum was clear cut and the tip of the catheter beneath the aortic valve was anterior to the septum and in the right ventricle Later films showed the tunneling of contrast medium through the defect and into the transposed aorta just as in Fig 4

Fig 6 shows the selective aortogram of an 8-year-old boy (W C.) with compli-

cating aortic insufficiency His other studies had shown that the shunt at the ventricular level increased the pulmonary blood flow to 2.5 times the systemic flow Pulmonary hypertension was but slight since there was infundibular stenosis (W C Table V) Intravenous angiocardiograms showed great dilution of contrast medium in the right ventricle so that details of the left heart were obscure However normal sequence of opacification of chambers and vessels was seen On selective aortography in the left anterior-oblique projection the tip of the catheter came to rest at the aortic valve which was far anterior When contrast medium was in







Fig 5 Pa ien \ F I I ra enous ngiocardiogram show normal sequence of opacification of the right heart and of the pulmonary artery *B* and *C* Selectiv right ventricular angiocardiograms show the tip of the catheter in the right ventricle, with the aorta opacifying above the right ventricle (*B*) nd not bove the left entricle (*C*)



Fig 6 Patient W C. Selective retrograde aortogram in left anterior-oblique projection shows the tip of the catheter near the aortic valve situated anteriorly and opacification of the ascending aorta with regurgitation into the right ventricle

jected the transposed aortic valve and aorta were visualized and the regurgitant flow was into the right ventricle not the left (Fig 6)

Catheter trajectory (Fig 7) in this same patient further confirmed the origin of both great vessels from the right ventricle for the catheter was passed in retrograde fashion through the aortic valve into the right ventricle and out the outflow tract into the normally placed pulmonary artery Neufeld[2] suggested another means by which the position of the aortic catheter should suggest this anomaly With two catheters, one introduced from the right heart into the pulmonary artery and the other introduced through the aorta in retrograde fashion to the aortic valve the left anterior-oblique projection revealed that the aortic valve was anterior and in the same coronal plane as the pulmonary artery

Because of the dilution of contrast agent by the left-to-right shunt at the ventricular level intravenous angiocardiography provided pictures which were less clear-cut than those of the selective studies, but which sufficed to demonstrate the transposed aortic valve in retrospect in Je V (refer to Fig 2) and on search for it in 7 other patients. In 1 of these (J F) who was being considered for surgery this study led to the correct preoperative diagnosis and to successful repair[5] In only 2 patients did intravenous angiocardiography demonstrate premature opacification of the aorta

Surgical considerations

Four of these patients with increased pulmonary blood flow were subjected to operation The unfortunate experience with the first 2 before the malformation was recognized or understood made it clear that to close the defect directly by sutures was to be avoided Instead a hammock like prosthesis was needed which would encircle the base of the aorta anteriorly and could be sutured to the sides and inferior aspect of the defect, thus leaving the aorta in unobstructed continuity with the left ventricle yet interrupting the interventricular communication[1,4,5] Such a hammock would provide a floor for the tunnel by means of which blood already streamed through the defect and out the aorta Review of autopsy material showed that this was feasible

The operation was performed successfully on J F[5] The results of her three cardiac catheterizations, two preoperatively and the third performed 18 months postoperatively are shown in Table VI The postoperative study indicated almost complete abolition of the shunt and a



Fig 7 Patient W C. Course of catheter tip is advanced retrogradely through aortic valve into inflow portion of right ventricle and through outflow tract of right ventricle into pulmonary artery

decrease by half in the right ventricular hypertension. Although the infundibulum was not resected at the time of the operation, the right ventricular–infundibular systolic gradient lessened. Persistence of some pulmonary hypertension was due to persistent elevation of pulmonary vascular resistance.

The second patient in whom a diagnosis was made preoperatively, W. C., was operated upon in 1962 when heart failure had developed and proved to be difficult to control. He had coexistent aortic insufficiency. During cardiac bypass, the large regurgitant flow through the aortic valve made it necessary to cross-clamp the aorta frequently and for long periods while the hammock was sutured into place. Then, through an aortotomy, the cause of the aortic insufficiency—a hole in one of the leaflets—was identified and repaired. The perfusion was of necessity a prolonged one, and the patient did not maintain an adequate cardiac output afterward. The operation and the subsequent autopsy confirmed the diagnosis.

It is significant that, at operation, only in the last child was the position of the aorta clearly anterior. In this instance the anterior location was exaggerated by enormous cardiac enlargement and clockwise rotation of the heart. In the first case the aorta was noted to be situated somewhat more anteriorly than normal although not enough to cause suspicion that it was transposed. In the second case the aorta did not appear to be unusual either by external inspection at operation or at autopsy. Even in J. F., in whom the diagnosis was made before operation, some observers in the operating room were confused by the anatomy and could not tell by external inspection the abnormal relationship of the aorta. Similarly, on review of the postmortem specimens, the external relationship of the two great vessels sometimes appeared grossly to be normal, whereas in others the aorta appeared to be slightly anterior and lay just to the side of, rather than just posteromedial to, the pulmonary artery. This subtle difference and sometimes misleading external appearance at operation and even at autopsy[3] emphasize the need for preoperative recognition of the anomaly.

An additional surgical consideration is the unusual position and course of the right coronary artery, which traverses the area of incision for the usual right ventriculotomy. For this reason, as well as because of the posterior location of the septal defect, the repair was made through an atriotomy in the latter 2 patients.

Associated conditions

Aortic insufficiency. The boy with complicating aortic insufficiency has already been mentioned. The regurgitation was due not to an unsupported aortic cusp, such as occurs with ventricular septal defect and normal aortic origin, but to a hole in the center of one leaflet. Presumably, this was acquired as a result of subacute bacterial endocarditis, for he gave a history of a febrile illness treated for several weeks with penicillin at the age of 5 years. It was after this illness that a diastolic murmur was first noticed and he was referred to The New York Hospital with a tentative diagnosis of patent ductus arteriosus.

Pulmonary stenosis. Patients with severe pulmonary stenosis have been excluded from this review, for our present purpose is to demonstrate the manner in which transposition of the aorta with subaortic

Table VI

	Age (yr.)	Pressures (mm. Hg)			PBF/SBF	Systemic oxygen saturation %
		RV	PA	SA		
Preop.	7	74–85/7	71/42	94/54	1.5	87
	10	97/3	57/34	97/61	1.6	93.1
Postop.	11.5	55/3	43/13	112/70	1.1	96.6

ventricular septal defect masquerades as acyanotic typical simple ventricular septal defect However 2 patients had systolic pressure gradients across the infundibulum of 32 mm Hg (J F) and 81 mm Hg (W F) In both the infundibular stenosis was relative rather than real and was probably due to increased right ventricular outflow of blood and hypertrophy of the outflow tract for neither patient had evidence at operation of a fixed obstruction Without surgical removal of infundibular tissue the gradient was reduced to only 12 mm Hg at postoperative catheterization in J F At autopsy in W C the outflow tract of the right ventricle was dilated and capacious, without evidence of the obstruction that had been demonstrated physiologically during life

Mitral valve anomalies Neufeld and associates have pointed out the abnormal arrangement of the mitral valve in this malformation either the anterior mitral leaflet was elongated as it stretched through the defect to adjoin the aortic valve or else this leaflet was attached to the septal defect or septal leaflet of the tricuspid valve but was not in continuity with the aortic valve Clinical manifestations of this disturbed relationship were evident in only 1 patient J C who had a murmur of mitral stenosis and left atrial enlargement out of proportion to the enlargement of the other chambers. Right heart catheterization added confirmation of obstruction of left atrial outflow for the pulmonary capillary pressure was elevated to 15 mm Hg and the tracing showed a prominent a wave of 21 mm Hg This boy followed since heart failure early in infancy responded to medical management and is doing well at age 4 Surgery has not been undertaken

Corrected transposition Not included in this review is the case of an 18-year-old acyanotic girl who died of subacute bacterial endocarditis. Both great vessels arose from the venous ventricle in the relationship of "corrected transposition" The ventricular septal defect was quite large Functionally the malformation was the same as that under discussion

Miscellaneous cardiac anomalies Jo V had evidence at catheterization of a shunt at the atrial level and had no inferior vena cava but drainage through the azygos system C. R who died at the age of 7 months had a secundum type of atrial septal defect The ductus arteriosus was patent in those who died as a fetus or newborn infant.

Noncardiac anomalies or conditions Just as in the case of infants who died with a ventricular septal defect and normal aortic origin 6 infants who died had other anomalies 5 with nonlethal abnormalities of the genitourinary system 4 with skeletal deformities and 2 with neurological abnormalities Two babies had cataracts and the mother of one of these had had rubella in the first 2 weeks of pregnancy

The pregnancy history was of interest in several other patients. The mother of A. F had grippe in the second month of pregnancy One baby was born after 6 years of infertility another after 4 previous miscarriages and 1 after three prior miscarriages Repeated bleeding in the first trimester was noted by 2 mothers.

Perhaps it is a coincidence but it is noteworthy that in this small group of 21 patients, several were born in crops." The 3 stillborn premature infants were delivered within 4 days of each other in July 1954 Two were born in October 1956 and 2 others were born in June, 1961 The two oldest living patients were born in the early summer of 1942. In all 16 were born between May and October which suggests the possibility of an infection early in pregnancy in the fall and winter months.

Discussion

To name this particular malformation is now more difficult than to diagnose it. The term double-outlet right ventricle [4] is appropriate but not precise since there are other situations in which the right ventricle has a double outlet for example the Taussig Bing malformation The important difference in these two conditions is that, in the anomaly under discussion the ventricular septal defect is subaortic so that oxygenated blood from the left ventricle streams into the aorta and the patient is not visibly cyanotic In the Taussig Bing heart the septal defect is beneath the pulmonary artery so that vessel receives more of the stream of oxy

genated blood from the left ventricle and the aorta receives the mixed arterial and venous blood of the right ventricle. The patient is cyanotic.

To name the anomaly "origin of both great vessels from the right ventricle without pulmonary stenosis"[7,3] helps in an understanding of the physiology but will not include all patients who function alike. For example, this classification would eliminate 2 of the present patients (J. F. and W. C.) who had pressure gradients significant of pulmonary stenosis, yet had increased pulmonary blood flow and whose condition masqueraded as acyanotic ventricular septal defect.

To call it "simple transposition" as Spitzer[1] did is not sufficiently informative, whereas to name the anomaly "ventricular septal defect with transposition of the aorta" is not strictly correct if one accepts the phylogenetic theory of Spitzer and the still earlier work of Peacock.[19] These and other theories of transposition of the cardiac vessels were reviewed by Harris and Farber[22] in 1939.

Although the clinical behavior of this anomaly was new to us when we unexpectedly first encountered it, Peacock a century earlier knew that the malformation existed and interpreted the anomaly in relation to comparative anatomy. He pointed out that "the sinus and infundibular portions of the right ventricle in man are the analogues of the right systemic and pulmonic ventricles of the turtle. In the turtle there is a right ventricular aorta as well as a left ventricular aorta. He stated that the ventricular septal defect between the subaortic region of the left ventricle and the sinus of the right ventricle was homologous with the foramen between the two aortic ventricles of the turtle. In the malformation in which both the aorta and pulmonary artery arise from the right ventricle, Peacock said that "the analogy to the form of the heart in Chelonia is most decided, the aorta arising from the one cavity—the sinus of the ventricle—and the pulmonary artery from the other—the infundibular portion or conus arteriosus."

In the nineteen-twenties, Spitzer classed this malformation as Type 2 of five types of transposition. He called it "simple transposition of the aorta." He too related the malformation to the stage of double aorta. He stated that an increased amount of detorsion took place, removing the left aorta from its connection with the left ventricle. The left aorta was obliterated as flow through it ceased, whereas above the right ventricle the right aorta, which normally should be obliterated, reopened instead. Both the aorta and pulmonary artery thus arose from the right ventricle. In this interpretation, the apparent transposition of the aorta is due to closing of the left aorta and opening of the right aorta so that no true transposition occurred. In view of this concept the term "ventricular septal defect with right ventricular aorta" would be appropriate.

Grant[14] has recently proposed a new way of looking at the transposition complexes based on a study of the ventricular skeleton. He postulated a shift in orientation of the fibroplastic continuum which lines the primitive heart and extends from the A-V canal to the truncus arteriosus. Application to this anomaly would suggest that the fibroplastic continuum was interrupted by musculature so that division of the A-V canal was not continuous with that of the truncus. Since the truncus was not held to the mitral ring, the left ventricle acquired no truncal outlet, but the right ventricle acquired two when the truncus divided.

Perhaps the most suitable designation for the anomaly is ventricular septal defect "with right ventricular aorta" or "with both great vessels from the right ventricle," but in either instance an additional qualifying statement is needed in regard to the presence or absence of cyanosis. This, in turn, relates to the location of the septal defect and to the status of pulmonary blood flow. The following classification is suggested.

Ventricular septal defect with right ventricular aorta or with both great vessels from the right ventricle. (1) *Acyanotic.* Subaortic ventricular septal defect with increased or average pulmonary blood flow. (2) *Cyanotic.* (a) Subaortic ventricular septal defect with (1) severe pulmonary stenosis, (2) severe pulmonary vascular obstruction. (b) Subpulmonary ventricular

Summary

Acyanotic ventricular septal defect with both great vessels from the right ventricle mimics a simple ventricular septal defect and is less rare than previously believed. The possibility of right ventricular origin of the aorta should be considered when the patient with a ventricular septal defect has a right ventricular pressure at a systemic level. The diagnosis can be made by contrast visualization in the left anterior oblique projection. Surgical repair has been accomplished using a hammock-like prosthesis which interrupts the interventricular shunting and permits unobstructed flow from the left ventricle to the aorta.

We wish to express our appreciation to the following physicians who assisted us in completing the data on some of these patients: Dr. Howard Burchell, Rochester, Minn., Dr. Charles Kossmann, New York, N. Y., Dr. Rodolfo Kreutzer, Buenos Aires, Argentina, and Dr. Leonard Steinfeld, New York, N. Y. Dr. Kathryn H. Ehlers, Dr. Tomiko Ito, and Dr. Harry Foster of the Pediatric Cardiology staff gave valuable assistance in the evaluation of the patients. Dr. Wallace Campbell and medical student William Deely and William Robertson helped in the review of postmortem specimens.

Addendum

After this paper had been submitted for publication, two additional instances were encountered at autopsy in infants who died in heart failure, and the diagnosis was made during life in a 10-year-old boy.

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Experimental and laboratory reports

Studies in a cardiovascular model on the arterial dilution curve of valvular regurgitation

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With mitral regurgitation, indicator dilution curves have an earlier appearance, lower peak, flatter downslope, and wider spread if the incompetent valve lies between the injection and collection sites. Many methods of assessing regurgitation are based on these changes. Such methods include a variety of semiquantitative indices[2-4] and attempts at quantification.[5-] The present study was designed to determine what hydrodynamic phenomenon these methods actually measure.

In addition, the observations of Korner and Shillingford[-8] that changes in forward flow or in volume traversed can simulate some but not all of the effects of regurgitation have suggested that there is some specific effect of regurgitation or that the total effect of regurgitation on a dilution curve might be unique. The second purpose of this study was to test that implication.

Moreover, factors other than flows and anatomic volumes can influence the curve and modify the effects of regurgitation. These nonspecific factors include, among others, changes in chamber geometry, as shown by Hoffman and Rowe, and by Hoffman and Shillingford, and changes in the location of injection and collection sites, as shown by Korner and associates.[11] The third purpose of this study was to determine a common denominator for these nonspecific influences, to define this in conventional hydraulic terms, and, if possible, to express it quantitatively.

Materials and methods

A simple model of a two-chambered pulsatile heart was constructed. The ventricle consisted of a glass syringe, the total volume, stroke volume, and end-systolic volume of which could be precisely adjusted, and the stroke rate of which could

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be varied The ventricle was connected by means of a double valve assembly* to a rubber aorta, and to an atrium the volume shape and elasticity of which could be varied The atrium was connected by polyethylene tubing to a water reservoir At the atrial end of the tubing a portal was provided for the injection of Evans blue dye The aorta was connected to a second reservoir in which net forward flow was collected and measured

One hundred and seventeen experiments were performed In all the aortic valve was competent In 56 experiments the atrioventricular valve was also competent In these experiments the minute flow collected from the aorta agreed within 2 per cent with the product of stroke volume and stroke rate In 61 experiments, mitral incompetence was present with regurgitant flows ranging from 8 to 73 per cent of total ventricular output. In these experiments forward flow was measured directly by collection of aortic effluent and regurgitant flow was calculated as the difference between total ventricular output (stroke volume × stroke rate) and forward flow

Dilution curves were obtained by drawing a portion of the aortic outflow through a cuvette densitometer[10] the output of which was recorded continuously on an oscillographic recorder Fig 1 illustrates pertinent features of the curves. Duration of injection was less than 0 3 second In order to enhance the reliability of measurements from the recorded curves, we selected the amounts of dye injected and the sensitivities of the densitometer and recorder to give peak deflections of at least 100 mm Since there was no recirculation the descending limb approached (and if flow and recording were continued reached) the base line Between experiments, the system was thoroughly flushed In all experiments the heart rate was 60 per minute the sampling rate was 0 17 ml per second and the dead space of the sampling system (including the densitometer cuvette) was 0.25 ml The characteristics of the system satisfy the figure of merit for catheter sampling derived by Sherman and associates.[1]

*The valve assembly used was a modification of their Cornell valve assembly supplied by Becton-Dickinson Co Rutherford, N J

All dilution curves were plotted semilogarithmically and concentration was extrapolated to 1 per cent of peak value For each experiment the parameters indicated and defined in Fig 1 were measured or calculated In addition mixing volume was calculated according to Newman[11] and central volume was calculated as the product of mean circulation time and forward flow[12] Time measurements were corrected for the delay in the sampling system Variance as a measure of spread was selected as the parameter to be related to flows and volumes because it has been shown[4] to be the parameter of choice in applying the method of Korner and Shillingford The several regression equations relating variance to forward flow and mixing volume or to forward flow and central volume were derived using standard mathematical techniques.[6]

Results

Fig 2 illustrates the well known effects of mitral incompetence. With forward flow central volume and atrial geometry and elasticity kept constant the introduction of mitral regurgitation resulted in an earlier appearance time, lower peak concentration flatter downslope and increased spread

That this combination of effects is not unique to mitral regurgitation is shown by experiments illustrated in Figs. 3 4 and 5 With the mitral valve competent and with forward flow and central volume constant alteration in atrial mixing produced by substituting an elastic chamber for the original rigid atrium resulted also in earlier appearance lower peak flatter downslope and wider spread (Fig 3) The same result could be produced by redistributing fluid between atrium and ventricle so as grossly to enlarge the dominant mixing volume In fact by so doing it was possible in the presence of competent mitral valves to produce curves which appeared to be more regurgitant than those obtained with mitral insufficiency (Fig 4) Enhancement of atrial mixing by the substitution of a polyhedral atrium in which turbulence was evident for a cylindrical atrium in which streamlining was evident also produced these changes. Fig 5 shows the results of two studies

one with a competent and one with an incompetent mitral valve with forward flow and central volume virtually identical, in which by altering the determinants of atrial mixing we could produce curves of almost identical contour and appearance time

The intimate relation between alterations in mixing and deformity of the curve associated with regurgitation is shown by experiments illustrated in Figs. 6 through 10 From a series of normal studies, an equation was derived which expressed the relation between variance forward flow and central volume Fig 6 shows the nomogram for that equation When mitral incompetence was introduced the observed spread exceeded that predicted for the prevailing forward flow and central volume (Fig *7A*) It should be noted that variance serves as a convenient representative of the complex of deformities seen with regurgitation, since with area (flow) and mean circulation time (central volume) constant wider spread was uniformly associated as would be expected with earlier appearance later disappearance and lower peak. Under the conditions of Fig *7A* semiquantitative indices can correctly distinguish normal cases from those with regurgitation and estimates of backward flow by the Korner and Shilling

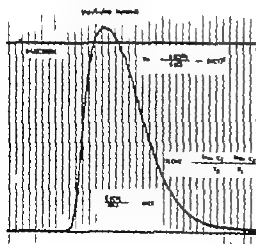


Fig. *1* Indicator-dilution curve recorded in the absence of alvular regurgitation. *T* Time, *C* Concentration *AT* Appearance time. *MCT* Mean circulation time *C* Peak concentration. *V* Variance.

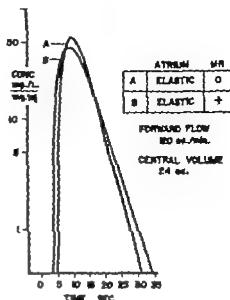


Fig. The effects of regurgitation at the atrioventricular valv on the dilution curv recorded downstream to the aortic valve.

ford method are substantially correct. However when appropriate changes in distribution of volume or in atrial elasticity or geometry were introduced (Fig *7B*) the system with regurgitation could behave like the normal and the normal system like one with an incompetent valve.

That mixing is the common denominator is shown by the analysis illustrated in Fig 8. All of the cases used to construct the nomogram of Fig 6 had a mixing volume between 16 and 24 per cent of central volume All subsequent studies with a comparable ratio of mixing volume to central volume fell on that nomogram whether or not regurgitation was present If mixing was increased whether by regurgitation or by change in the properties of the model a new relation prevailed between variance forward flow and central volume indicated by a line of similar slope but different intercept For each such new relationship there was no distinction between normal and regurgitation Thus, for a given forward flow with or without regurgitation variance is related to central volume not by a single regression line but by a family of such lines, each uniquely determined by the ratio of mixing volume to central volume If this be the case however a simpler relationship prevails

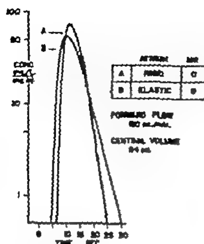


Fig. 3 The effect of alteration in atrial elasticity on the arterial dilution curve.

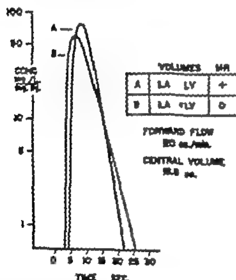


Fig. 4 The effect of volume redistribution on the arterial dilution curve.

for a given forward flow with or without regurgitation variance is a function of mixing volume

Using the same series of normal studies from which the equation was derived relating variance to forward flow and central volume we derived a second equation which related variance to forward flow and mixing volume. All other studies fitted the nomogram which corresponded to that equation whether regurgitation was absent (Fig 9A) or present (Fig 9B) It is recognized that in mitral regurgitation Newman's slope volume cannot be equated with the mixing volume of a single chamber but is a complex function of the volumes of atrium and ventricle and the regurgitant bolus.[17] However as a determinant of the dilution curve this function behaves as a virtual single volume from which indicator is being washed In this sense the foregoing data demonstrate that the parameters of dilution curves with or without regurgitation can be described as functions of forward flow and of an effective mixing volume.

This conclusion and its practical significance are illustrated for the entire series of 117 cases in Fig 10 As curve distortion (earlier appearance lower peak and flatter downslope) increases observed spread increasingly exceeds that predicted for the prevailing forward flow and central volume and the estimate of backward flow must increase. Semiquantitative indices to the severity of regurgitation will necessarily also depart increasingly from the normal However distortion of the curve parallels the ratio of mixing volume to central volume and at any level of this ratio no distinction is possible between normal cases and cases of regurgitation.

Discussion

From these results it is clear that the effects of regurgitation on downstream dilution curves, after injection upstream

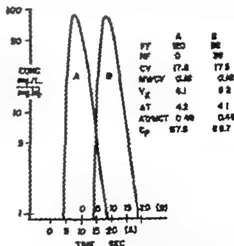


Fig. 5 Qualitatively and quantitatively indistinguishable dilution curves produced in the presence (A) and absence (B) of competent mitral valve FF Forward flow RF Regurgitant flow Other abbreviations as in Fig 1

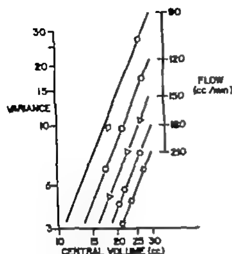


Fig. 6. Nomogram showing the relationship between variance, central volume, and forward flow.

to the incompetent valve are not specific for that lesion but can be entirely duplicated by a change in mixing. This conclusion is supported also by the work of Thorburn and associates,[8] who state that instead of being able to characterize normal curves in the absence of valve incompetence by a single regression equation, the results suggest that these normal curves can be specified by a family of equations having similar regression coefficients and differing only in intercept values. Thus, any arterial dilution curve characterized by a particular area, peak, mean circulation time slope, and variance, is explicable as the resultant of at least two systems one of which entails the presence of mitral regurgitation and the other its absence. (It is in this sense that Newman's mixing volume or its derivative, the residual volume is applicable conceptually in mitral regurgitation although Newman's volume has no discrete anatomic reference in this lesion, the dye curve is entirely explicable in terms of washout at a given stroke rate and stroke volume from a system with a dominant chamber having the Newman volume as its end-diastolic volume.)

It follows that direct measurement of backward flow from a single distal dilution curve after proximal injection is not possible. Polissar and Rapaport from a theoretical analysis of indicator-dilution curves produced by a pulsatile two-chambered mathematical model have offered a proof of this conclusion by demonstrating that the experimental curve gives an insufficient number of equations relative to the number of unknowns and therefore an indeterminate solution.

Although a valid direct measurement of backward flow cannot be made from such curves it is theoretically possible to make

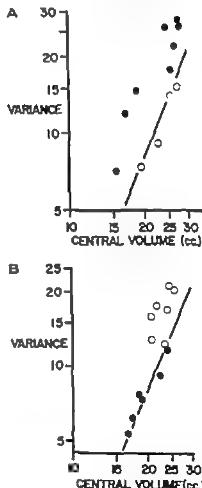


Fig. 7. The effect of alterations in mixing on the relationship between variance flow and central volume in the presence and absence of mitral regurgitation. In this figure and in Figs. 8 and 9 the open circles represent cases without regurgitation and the solid circles represent cases with regurgitation for simplicity and clarity the data shown are those obtained at a forward flow of 120 ml. per minute. The line in the present figure is the regression line for that flow from the nomogram of Fig. 6. In the studies shown in *A* the physical properties of the model were the same as those in the studies used to derive the nomogram. In *B* volume distribution, atrial geometry or atrial elasticity had been changed.

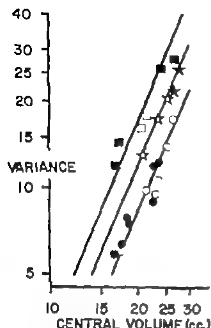
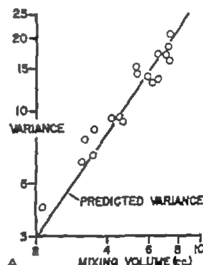


Fig 8 The relationship between variance central volume, and the ratio of mixing volume to central vol me The lowest of the three lines is the regression line for a forward flow of 120 ml. per mi ute, from the omogram of Fig 6. The circles clustering bout that line represent cases in which, like those pon which the nomogram was based, MV was 16 to 24 per cent of CV the stars represent cases in which MV was 27 to 30 per cent of CV and the squares represent cases in which MV was 33 to 37 per cent of CV

a statement concerning the probability of the presence of regurgitation This can be accomplished by comparing the relationship between several parameters in a given case with the relationship usually prevailing between these parameters in non regurgitant cases. There is, as Polissar and Rapaport have pointed out no necessary incompatibility between a theoretical demonstration of mathematical indeterminacy and an experimental demonstration of empirical efficacy Equations may be constructed which permit a statistically satisfactory prediction of slope for example from only two parameters even though it be known that three parameters are required to define slope accurately If the relationship prevailing in nonregurgitant cases between area (flow) mean circulation time (central volume) and variance or slope (mixing) is expressed by a regression equation the extent of departure from this relationship in a given case is a statistical statement as to the probability that this case is drawn from the normal population If this is improbable mitral regurgitation is diagnosed and the extent of improbability is a prediction as to the severity of regurgitation

If enhanced mixing can simulate the effects of mitral regurgitation it must be asked whether the effects observed in experimental and clinical mitral regurgitation are due to enhanced mixing With forward flow and anatomic volume held constant regurgitation can have three effects (1) Whether or not mixing is complete regurgitation serves as a residual



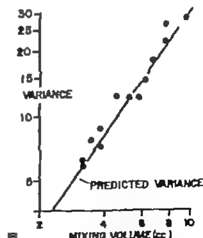


Fig 9 The relationship bet een variance and mixing volume i the absence (A) and in the presence (B) of mitral regurgitation The line i the regression line for a forward flow of 120 ml per minu t from nomogram relating variance to forward flow nd mixing vol me

volume limiting the rate at which indicator is moved forward from a chamber. The collection site cannot, after all, distinguish dye which has been retained from dye which has been moved retrograde. Thus, in mitral regurgitation if atrial residual volume were to become zero the regurgitant volume would act solely as a component of ventricular residual volume. (2) Whether or not mixing is complete regurgitation serves as a flow distributing indicator to otherwise inaccessible mixing sites. Thus in mitral regurgitation back flow delivers dye to an atrium already traversed. (3) If mixing in either chamber is incomplete mitral regurgitation serves to augment mixing tending to make the volume of dispersion in each chamber approach as a limit the anatomic volume of that chamber. If the dominant (i.e. larger) mixing volume is thereby enlarged or the nondominant volume transformed into the dominant then the ratio between Newman's mixing volume and Hamilton's central volume will be increased.

The first two effects the implications of which have been pointed out by Mc Clure and associates, apply as has been stated whether or not mixing is complete and are inevitable in mitral regurgitation since they are present by definition. The third effect requires that mixing be incomplete in the absence of regurgitation and is not inevitable. However much experimental evidence attests to the fact that this effect is the major determinant of the arterial dilution curve in mitral regurgitation. That mixing in cardiac chambers is normally incomplete has been shown by cinefluorography in dogs[19,21] and by indicator-dilution studies in vitro[22] in intact dogs,[21,22] in congenital heart disease,[24,26] and in disease of the mitral valve.[22,27] That mitral regurgitation enhances mixing has been suggested on the basis of indicator-dilution studies in man and has been documented photographically in a hydraulic model[29] and radiographically in vivo.[21] Moreover the relative importance of this effect as compared with the first two is shown by the fact that systems which ensure complete mixing are little affected by the introduction of incompetence. Levison and associates,[30] using an electronic analog of a two-chambered heart to display wave forms simulating dilution curves, found that the shape of the curves was strikingly affected by changes in chamber volumes, but relatively insensitive to changes in atrioventricular regurgitation. Phinney and associates,[29] in a two-chambered hydraulic model showed that with mechanically augmented mixing produced by a rotating paddle the addition of valvular incompetence equal to twice the forward flow produced no further significant changes in the form of the curve. Polissar and Rapaport's mathematical model which posited completeness of mixing demonstrated the same insensitivity to the volume of retrograde flow if all else was held constant.

Thus, in mechanical, electrical and mathematical analogs of the left heart, the gross changes in contour seen in clinical mitral regurgitation in animal experimentation and in most hydraulic models are shown to be reproducible only by changes in forward flow or chamber volumes, or if these are held constant, by augmentation of mixing.

This analysis has certain important implications. Methods which assess mitral regurgitation from distal dilution curves after proximal injection cannot directly measure regurgitant flow. They can how-

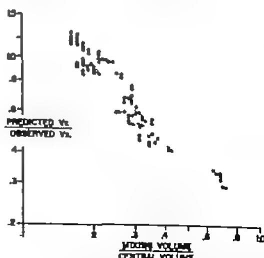


Fig. 10. The relationship between curve distortion and mixing. Distortion of the curve is represented on the ordinate by the ratio of predicted variance to observed variance. The degree of mixing is represented on the abscissa by the ratio of mixing volume to central volume.

ever provide an estimate of the severity of insufficiency Their efficacy in so doing must depend upon a useful but fortuitous empirical relation between enhancement of mixing and the magnitude of backward flow Optimal usefulness, therefore requires that other factors which may influence mixing are not affected concomitantly Thus in acute studies in animals backward flow may be estimated with creditable accuracy[21] since there is no necessary accompanying change in shape elasticity or volume distribution of the cardiac chambers. However in chronic clinical mitral regurgitation in which changes in the volume shape and elasticity of the chamber are virtually inevitable and may themselves be a function of the severity of the lesion evaluation of regurgitation from single downstream dilution curves is at best semiquantitative and approximate[22-25]

It follows, moreover that despite the acknowledged if limited diagnostic utility of such methods the application of them to clinical investigation of the pathophysiology of valvular regurgitation is hazardous and probably unjustified Their reliability is questionable for example in studies of the influence on regurgitation of cardiac decompensation drugs, exercise or other departures from the steady state.

This analysis may also explain the less striking deformity of dilution curves seen in aortic insufficiency than in comparable degrees of mitral insufficiency[26] In its behavior as a flow the regurgitation in mitral disease distributes dye between two mixing chambers, whereas in aortic regurgitation the distribution is between a true mixing chamber and a conduit Moreover left ventricular mixing is normally better than atrial mixing[27] so that augmentation of mixing is a less potent determinant Indeed if left ventricular mixing were initially complete and the aorta were the site of no mixing at all the backward flow in aortic insufficiency would behave exclusively as a component of ventricular residual (end-systolic) volume

Summary

Many methods for assessing valvular regurgitation, including techniques which attempt to quantify backward flow are based on analysis of deformities characteristically observed in arterial dilution curves. The present study was designed to ascertain what these methods actually measure

Dye was injected into the atrium and dilution curves were recorded continuously from the elastic aorta of a pulsating two-chambered cardiovascular model Forward flow backflow ventricular stroke and end-systolic volumes and atrial size shape and elasticity were systematically varied One hundred and seventeen experiments were performed In 61 experiments the atrioventricular valve was made incompetent with backward flows ranging from 8 to 75 per cent of total ventricular output.

With forward flow and central volume held constant enhancement of mixing produced by altering atrial geometry or the distribution of fluid between atrium and ventricle reproduced the earlier appearance lower peak flatter downslope and wider spread seen with valvular regurgitation Qualitatively and quantitatively indistinguishable dilution curves were produced in the presence and absence of regurgitation by appropriate manipulation of mixing For a given forward flow with or without regurgitation the spread of dilution curves was related to Newman's mixing volume by a single regression line but to Hamilton's central volume by a family of such lines, each uniquely determined by the ratio of mixing volume to central volume. With forward flow and mixing volume held constant, the dilution curve was unaltered by the introduction of valvular regurgitation

These results demonstrate the following (1) The parameters of dilution curves obtained downstream to a valve after injection upstream are functions of forward flow and of a volume real or virtual in which indicator has effectively mixed whether or not valvular regurgitation is present. (2) Methods which assess valvular regurgitation by analysis of such curves do not measure regurgitant flow They are merely indices of an enhanced mixing which usually but not inevitably accompanies regurgitation

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Dynamics of normal and diseased cardiac valves

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Normal cardiac valves offer minimal resistance to the forward flow of blood and establish a unidirectional circulation by effectively preventing the back flow of ejected blood. When diseased, these valves may prevent complete emptying of the cardiac chambers or may permit reflux of ejected blood, thereby producing progressive cardiac dilatation with serious impairment of myocardial function.

Postmortem observations, by disclosing pathologic valve structures, have played a basic role in the development and evaluation of heart surgery. The value of these observations has been increased by McMillan,[1] who, in order to better correlate structure with function, designed the technique of cardiac pulse duplication for the study of normal and diseased valves.

In the present communication, observations made with the technique of cardiac pulse duplication are correlated with previous work to explicate the structural factors essential for normal function of the cardiac valves, as well as the manner in which they are altered by disease. Previous reports have dealt with particular aspects of valve physiology or pathology but have not integrated the known facts into a single presentation. It is necessary to present these data in an integrated form since the clinical, radiologic, and hemodynamic manifestations of valvular disease are the direct result of the anatomic defect(s). Moreover, and most importantly, the type of anatomic lesion determines the corrective procedure to be employed. Hence, an understanding of the structure and function of normal and diseased cardiac valves is crucial in the selection of patients for cardiac surgery and in planning the therapeutic approach best suited for each patient.

Historical review

Late in the fifteenth century, Leonardo da Vinci studied the function of the aortic valve in beef hearts perfused with water.[2] He observed that this valve has a triangular orifice during systole, and he assumed that the sinuses of Valsalva are held partially open by eddies of fluid. In 1669, Richard Lower described the function of atrioventricular valves in animal hearts, and concluded that valve motion was passive. Senac, in 1749, studied the motion of the atrioventricular valves in living animals by transatrial palpation. In 1848, Parchappe noted that contraction of the papillary muscles exerts tension on the chordae tendineae and prevents eversion of the leaflets. See observed that during systole the septal leaflet of the mitral valve occludes most of the valve orifice. Lian

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observed that the sphincteric contraction of the ventricular myocardium furthers closure of the atrioventricular valves, an observation confirmed by Smith and co-workers in beating dog hearts. Kantrowitz bypassed the left chambers of beating dog hearts and noted that when the left ventricle is empty the sphincteric action of the myocardium about the mitral annulus does not suffice to close this valve. Fluid tight closure occurs only when fluid within the ventricle pushes up the leaflets and snaps them shut. Kantrowitz also found that during diastole the mitral leaflets are pulled open by the relaxing ventricle

With the cardiac pulse duplicator McMillan[3] obtained cinematographic records of functioning cardiac valves, and for the first time was able to evaluate objectively the results of surgical correction of aortic stenosis[13] He noted that attempted correction of aortic stenosis with a mechanical dilator produced torn and regurgitant valves maximal restoration of valve function was obtained when the fused commissures were divided with a knife under direct vision. In the cardiac pulse duplicator designed by Davila and co-workers[13] water is drawn into the ventricle from the atrium and expelled through the aorta by a piston pump connected to the ventricular apex. The forcible descent of the piston tends to snap open the mitral valve, and its ascent produces a paradoxical systolic expansion of the ventricle but otherwise does not appear to affect significantly simulated valve function. The Davila cardiac pulse duplicator has been ingeniously modified by Hargett and Everest[13] who applied external cyclic pressure to the heart by surrounding it with a water jacket connected to a piston pump With this external cardiac pulse duplicator Frater[14] has studied in detail the anatomy and function of the canine mitral valve.

The McMillan cardiac pulse duplicator was modified by us in 195 to permit the simultaneous study of the aortic and mitral valves this modification was adopted by Kelley and co-workers[13] who determined forward and backward pressure gradients across stenotic aortic valves before and after surgical correction. Cardiac pulse duplicators have been used extensively in the development and evaluation of prosthetic valves for cardiac surgery[13]

In preliminary studies, cinefluorography coupled with angiocardiography has disclosed in detail the structure and function of cardiac valves in the living human being[17,3] Future developments of this technique would appear to require as a standard of reference correlated anatomic and physiologic studies of the type presented here.

Materials and methods

Fifty two human hearts obtained at autopsy were perfused by means of a McMillan cardiac pulse duplicator[3] modified to permit the simultaneous study of the mitral and aortic valves (Fig 1) With it, fluid under pressure enters the left ventricle during simulated systole closes the mitral valve and leaves through the open aortic valve. During simulated diastole fluid rapidly leaves the ventricle, opens the mitral valve and snaps the aortic valve closed The flow of fluid delivered to the heart by a centrifugal pump is controlled by "systolic" and diastolic solenoid valves The aortic outflow is provided with an air chamber to simulate arterial elasticity and with a valve to control peripheral resistance and flow Left atrial filling and pressure are maintained by an independent reservoir placed above the atrium. The two solenoid valves are regulated by an electronic device which also controls heart rate and length of systole

Hearts were prepared by dividing the aorta 4 0 cm. above the aortic valve and the other great vessels flush with the heart. The visceral pericardium was carefully perserved since it gives substantial mechanical support to the myocardium Both coronary arteries were ligated to prevent leakage. The orifices of the pulmonary veins were joined by an incision clots were washed out and the atrium and mitral valve were inspected and palpated. A viewing chamber placed immediately above the mitral annulus was attached to the atrium with a lung tourniquet A second viewing chamber was attached to the aorta with silk ligatures. An orifice made in the ventricular apex was cannulated with a flanged glass tube Aortic outflow was

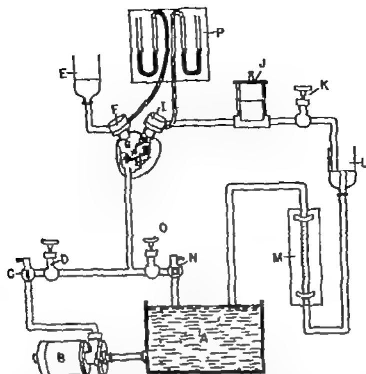


Fig. 1 Modified McMillan cardiac pulse duplicator. *A*, water reservoir; *B*, centrifugal pump; *C*, systolic solenoid valve; *D*, inflow control valve; *E*, bubble trap; *F*, plastic viewing chamber for mitral valve; *G*, left auricle; *H*, left ventricle; *I*, plastic viewing chamber for aortic valve; *J*, closed chamber to simulate arterial elasticity; *K*, peripheral resistance control valve; *L*, open reservoir to convert pulsatile flow into continuous flow; *M*, flowmeter; *N*, diastolic solenoid valve; *O*, diastolic outflow control valve; *P*, manometers.

measured with a rotameter. Colored cinematographic records were obtained with a 16-mm. reflex camera operated at a shutter speed of 24 frames per second.

Results

Normal atrioventricular valves. In 6 normal hearts the mitral and tricuspid valves opened and closed rapidly and completely during each cycle (Figs. 2 and 3). At the onset of systole the sharp rise in intraventricular pressure lifted the valve leaflets, brought their free edges together and tightly sealed the inner third of their surfaces against each other. The chordae tendineae prevented the leaflets from everting into the atrium. In the mitral valve the septal leaflet occluded most of the valve orifice and was complemented by the mural leaflet and by the small anterior and posterior commissural leaflets (Fig. 2). In the tricuspid valve the anterior leaflet occluded most of the valve orifice and was complemented by the posterior and septal leaflets and by one or two small commissural leaflets (Fig. 3).

During diastole fluid pressure within the atrium caused a wide separation of the leaflets. Free commissures and thin supple chordae tendineae were essential for rapid and complete valvular opening.

Diseased atrioventricular valves. In 10 cases of rheumatic *mitral stenosis* valvular opening was impaired by one or a combination of three lesions (Fig. 4). The first lesion was fusion of the leaflets with obliteration of the commissures and commissural leaflets, which when extensive greatly reduced the diastolic valvular orifice. The second lesion consisted of fibrosis and calcification of the leaflets which transformed them into rigid shelves that occluded the mitral orifice. In the third lesion the chordae tendineae and papillary muscles were replaced by fibrous tissue which transformed them into rigid pillars



Fig. 2 Cy le of normal mitral al In systole the large septal leaflet occludes most of the orifice the leaflet edges mold aga nst each other nd the supple chordae tendinea prevent leaflet eversion. Flexible leaflets and patent ommissures permit complete diastolic opening



Fig. 3 C le of normal tricuspid al e. High perf sion pressures ha dilated the tricuspid ring nd produced mild insufficiency this al-o occurs hen the right heart dilates secondarily to aortic or mitral disease.



Fig. 4 "Fish mouth" mitral stenosis after al loplasty opening is f ll adequat nd insufficiency is not increased.



Fig. 5 Mitral insufficiency produced by retraction of the sept l leaflet nd shortening of the chordæ tendineae the valv cannot close during systole

that immobilized the leaflets. These fibrous pillars often narrowed the valvular channel and produced a second point of stenosis below the valve. When the fused chordae tendineae were separated there was noticeable improvement in leaflet mobility.

The effectiveness of mitral valvuloplasty in the treatment of mitral stenosis was evaluated in these hearts (Fig 4). Complete separation of the commissures and freeing of the chordae tendineae often increased the diastolic mitral orifice up to 2.5 square centimeters, when estimated visually. Digital estimates of the same orifices were usually about twice as great.

In 8 hearts *mitral insufficiency* resulted from marked fibrous retraction of the valve leaflets. The effect on the septal leaflet was most significant (Fig 5). These rigid and retracted leaflets closed slowly and could not seal off the atrioventricular orifice thus permitting regurgitation during systole. Fibrous shortening of the chordae tendineae anchored the leaflets



Fig 6 Normal aortic valve cycle Each cusp is cup-shaped and very flexible the systolic orifice is triangular



Fig 7 Bicuspid aortic valve resulting from fusion of one commissure the flexible free cusp permits opening and competent closure.



Fig 8 The same 1 after splitting of the fused commissures systolic opening is visibly improved.



Fig 9 Calcific aortic stenosis and insufficiency the cusps are retracted and fused together and the commissures are obliterated

in a semiopen position which produced marked mitral insufficiency Rupture of two or more chordae tendineae observed in 2 cases, produced marked mitral regurgitation by permitting systolic eversion of a leaflet into the atrium

In 3 hearts with severe mitral or aortic valvular disease there was dilatation of the *tricuspid* ring which impeded complete closure of the valves, and permitted regurgitation even though the valves were otherwise normal (Fig 3)

Normal semilunar valves In 5 normal hearts the pulmonic and aortic valves opened when intraventricular pressure exceeded arterial pressure. During systole the valve cusps separated completely from each other the sinuses of Valsalva remained partially open and the normal valve orifice was triangular (Fig 6) At the end of systole, intraventricular pressure fell suddenly and the cusps were snapped closed by the arterial pressure. All three semilunar cusps were essential for complete valve closure small defects in any one of them allowed large volumes of fluid under high pressure to regurgitate into the ventricle Flexibility of the free edges of the cusps allowed them to bend sharply at the center thus sealing the center of the valve orifice (Fig 6)



Fig 10 Rheumatic aortic insufficiency; fibrous retraction of the cusps makes diastolic closure impossible.

The normal cup-shape of each cusp results from the high point of attachment of its free edge to the arterial wall. This point of attachment converts the free edge of the cusp into a suspension band for the valve cusp and permits it to support high pressures. When the point of attachment was cut the cusp prolapsed into the ventricle, which resulted in marked insufficiency

Diseased aortic valves In 7 hearts with *aortic stenosis* the principal lesion was fusion of the commissures, which varied in type and degree. Slight functional impairment resulted from fusion of the outer third of the commissures. Complete fusion of only one commissure produced a bicuspid valve, but only a moderate amount of stenosis resulted if the remaining cusp was flexible (Figs. 7 and 8) When two of the commissures were fused the systolic blood was ejected through the remaining open commissure the resulting stenosis varied in severity with the degree of flexibility of the cusp margins which formed this open commissure When all three commissures were fused the valve orifice was central and rigid and concomitant insufficiency was

always present (Fig 9) under such circumstances marked calcification of the valve was the rule

In 6 additional hearts, large fibrocalcific deposits were present in all the sinuses of Valsalva but the commissures and cusps were intact the resulting stenosis was proportional to the size of these deposits. Careful debridement of these deposits produced remarkable improvement in valve function.

In 8 hearts with rheumatic *aortic insufficiency* the most frequent lesion was fibrosis with retraction of the free cusp edges, which kept them from closing completely (Fig 10) Retraction of even one valve cusp produced aortic insufficiency of 0.5 square centimeter or greater Dilatation of the aortic annulus with separation of the commissures and sagging of the cusps was observed in hearts with rheumatic aortic insufficiency and in 2 hearts with syphilis unequal sagging of the cusps and slow diastolic closure due to fibrosis furthered the insufficiency

Direct surgical relief of aortic insufficiency was evaluated under direct vision Circumclusion of the aortic annulus with a constricting silk band did not reduce the area of insufficiency Plastic and silk stents of variable size and shape were placed in the insufficient orifice to provide a substitute for deficient valve substance however the stents always migrated to the periphery of the valve orifice without relieving the insufficiency Prosthetic plastic valves with three cusps (designed by Dr Vannevar Bush) functioned satisfactorily when placed in the aortic annulus of several hearts (Fig 11) as did ball valves of the caged ball type [18]

Discussion

In the living organism the blood propelled by myocardial contraction transmits to the cardiac valves the energy that opens and closes them. Contraction of the myocardium surrounding the mitral and tricuspid annuli also plays an important role in the systolic closure of these valves. Closure of the atrioventricular valves is completed when the leaflets are brought together by the protosystolic rise in intraventricular pressure and is enhanced when the chordae tendineae are approximated by the contraction of the ventricles.[19]

Sphincteric contraction of the valvular annulus appears to be necessary for complete closure of the tricuspid valve but is not essential for competent closure of the normal mitral valve. Flexible and sufficient leaflet substance and intact commissures are indispensable for normal function of the atrioventricular valves, as shown here and elsewhere.[20]

In mitral stenosis, visual evaluation of finger fracture valvuloplasty[1] confirmed that this procedure relieved the stenosis and rarely produced insufficiency when properly performed Direct visual measurements indicated that after mitral valvuloplasty the valve orifice had been uniformly enlarged to greater than the functionally critical area of 1.5 square centimeters.[21]

Tricuspid insufficiency secondary to dila



Fig *11* Aortic plastic valve designed by Dr Vannevar Bush opening and closure are fully adequate.



Fig 9 Calcific ortic stenosis and insufficiency the cusps are retracted and f sed together and the commissures are obliterated.

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Transmural pressure and vascular resistance in soft walled vessels

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Application of the Hagen-Poiseuille formula to physiologic and clinical[1] problems has demonstrated a number of paradoxes in which experimental data deviate significantly from the expected pressure-flow relationships. For example, flow is negligible in some vascular beds until a threshold arterial pressure is applied.[2] In the lung, resistance falls as flow increases[3,4]; a rise in outlet pressure may also be associated with a decrease in calculated resistance.[7] In some organs, resistance may vary directly with the perfusing pressure (autoregulation).[8] These and other anomalies in pressure/flow relationships have been attributed to the influence of anatomic arrangements, vasomotion, wall tension, and viscous and turbulent effects of the stream.[11]

Some of the foregoing discrepancies may depend on the collapsibility of blood vessels. To extend the analysis of vascular resistance in collapsible vessels,[2] we have examined the relationship between transmural pressure and resistance in soft walled Penrose tubes.

Methods

Water from an arterial reservoir at a height P_A flowed through a segment of soft walled Penrose tubing to a venous outlet at a height P_V (Fig. 1). The Penrose tubing (diameter 0.62 cm., length 8 cm.) was enclosed in a glass capsule in which various extravascular air pressures, P_E, could be applied. The level of the Penrose tubing was the zero pressure reference. Intravascular pressures, P_I, were recorded at the outlet of the Penrose tubing; mean pressures were obtained by electrical integration. Flow was measured with a rotameter placed upstream to the Penrose tubing or by timed collection in graduated cylinders.

Resistance R was calculated as the drop in pressure in centimeters of H_2O from the source P_A to the collecting reservoir P_V divided by the flow in liters per minute Q so that

$$R = \frac{P_A - P_V}{Q}$$

Transmural pressure was determined as

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the intravascular pressure at the venous end of the soft walled vessel P minus extravascular pressure P_E When P_A was high oscillations of the intravascular pressure and of the drop in pressure across the soft walled vessel were observed at certain ranges of extravascular pressures intra vascular pressure was then estimated as the average of inlet and outlet pressures of the Penrose tubing

Results

1 Outlet pressures and flow at various P_E In these experiments, the vertical distance from P_A to P_V or perfusing pressure (Δ P) was held constant as P_V was raised from 0 to 50 cm H_2O At zero extravascular pressure, little effect on flow or on the caliber of the soft walled tube was observed as P_V was raised from 0 to 50 cm. H_2O (Fig 2, line at extreme right) When the outlet was at zero pressure (at the level of the Penrose segment) increases in extravascular pressure decreased flow (Fig 2 lines labeled 10 to 50 P_E) in some ranges of extravascular pressures the tube was observed to be closing and opening recurrently Under these circumstances elevation of the outlet resulted in an increased flow (Fig 2, compare flows as P_V is increased)

At outlet pressures which approached that of extravascular pressure, flow approached that obtained when the extra vascular pressure was zero When extra vascular pressures exceeded the height of the arterial reservoir ($P_E > P_A$) the Penrose vessel collapsed and flow was small For example, at $P_V = 0$ and $P_A = 30$ cm. H_2O flow is about 0.2 L. per minute when P_E is 50 or 40 cm H_2O (Fig 2)

2 Transmural pressure and flow By the use of P_V minus P as the ordinate scale, the data of Fig 2 could be gathered into a single curve In this form flow was relatively unaffected by elevation of the extravascular pressure until it was approximately 15 cm. above the outlet.

The sharp deflection in the tracing when the extravascular pressure was 15 cm above the level of the venous pressure suggested the possibility that the reservoir level did not accurately represent the pressure at the outlet of the soft walled vessel To clarify this, the pressure in the downstream end of the Penrose tube was measured directly with a needle. The difference between the intravascular pressure P and the extravascular pressure P_E represented the transmural pressure at the venous end of the Penrose tubing The relationship between transmural pressure and flow is shown in Fig 3 Changes in the slope of this tracing were observed when transmural pressure was zero or when a negative transmural pressure was numerically equal to the difference between the arterial and venous pressure heads (ΔP)

When transmural pressure was positive further increases in positive transmural pressure affected flow and resistance only slightly Flow decreased progressively however as transmural pressure became negative Stroboscopic observation of the soft walled segment demonstrated that it was closing and opening recurrently (flutter) When extravascular pressure exceeded the height of the perfusion reservoir the vessel wall collapsed completely and only a seepage passed through the collapsed tube

3 Transmural pressure and resistance Fig 4 shows the relationship between transmural pressure and calculated resistance. At positive transmural pressures the Penrose tubing was fully opened and

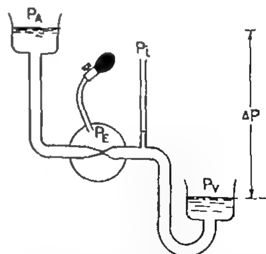


Fig 1 Design of the apparatus. An arterial reservoir source at a height P produced flow through soft-walled vessel enclosed in chamber shown as circle. The pressure in the extravascular compartment of the chamber is P_E. A venous reservoir at height P was the sink. The pressure gradient for flow P P is given as ΔP Extravascular pressure in the chamber could be adjusted by means of a syringe bulb.

resistance was relatively constant. As transmural pressure became progressively negative, either because of a rise in extravascular pressure or a fall in intravascular pressure the Penrose tube collapsed partially flutter then appeared and resistance increased progressively Finally when extravascular pressure exceeded arterial pres-

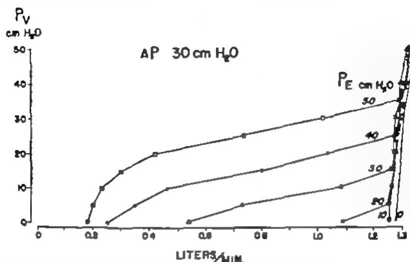


Fig 2 Effect of outlet pressure on flow ΔP was maintained constant t 30 cm. H_2O Flow is given in liters per minute in the abscissa the pressure of the outlet is given in cm. H_2O in the ordinate. The extravascular pressure P_E is given for 0 10, 20, 30, 40, and 50 cm. H_2O as indicated by the values adjacent to each of the lines. When P_E is zero flow increases but slightly as P is elevated. When P is zero, flow aries inversely with P_E. As P is elevated, flow increases, but especially if P is high. At P_V above 40 cm. H_2O all lines converge. Discussed in text

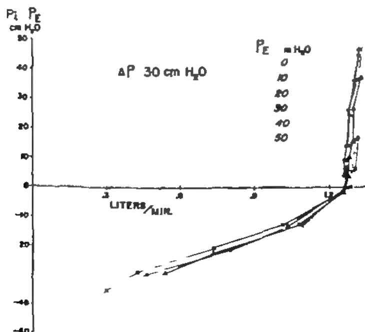


Fig 3 The data of Fig 2 are replotted against transmural pressure $P - P_E$ (intravascular minus extravascular pressure) measured at the venous end of the soft-walled t be.

sure, the vessel remained in the collapsed state and resistance was high.

Discussion

Most of the vessels of the body including those of the enteron and the genitourinary passages, as well as those of the cardiovascular and airway systems are collapsible Perhaps some of the difficulty in evaluating resistance to flow through these soft walled vessels has resulted from failure to consider the contribution of this property It is possible that results obtained on a soft walled latex tube may provide insights into the characteristics of flow in the soft walled vessels of the body

The present results demonstrate that resistance to flow through such soft walled vessels may vary greatly depending on whether they are filled or collapsed. When transmural pressure is positive the vessel is distended flow is rapid and energy losses and resistances are small and fairly constant. An increase in positive transmural pressure may distend the vessel further in accord with its compliance, and resistance may fall somewhat.

When a positive transmural pressure approaches zero as occurs when the outlet pressure is lowered or the extravascular pressure is raised the lumen may be incompletely filled, and flow for a given pressure head falls. *Hydrodynamic forces can* then generate an instability in which the vessel is thrown into recurrent oscillations[13] delivery will be affected by the proportion of each cycle that the vessel is open i.e., its "duty cycle," as well as by the diameter of the tubing during each opening period

When extravascular pressure exceeds intravascular pressure, the vessel is collapsed and flow is reduced If the outlet level is then raised to a point at which intravascular pressure equals extravascular pressure the cross section of the unstressed vessel will increase as it becomes rounded out and resistance will fall. If the collapsible vessels of the body behaved in a manner similar to the Penrose tubing of our model some of the anomalous behavior of the vascular resistance could be explained.

Effects of venous pressure When a soft walled segment is already distended elevation of the venous pressure has little effect on the calculated resistance As a rising outlet pressure distends a collapsed soft walled vessel such as a vein or capillary resistance decreases sharply[7,13] The fall in resistance in the lung on elevation of the venous pressure may result from similar

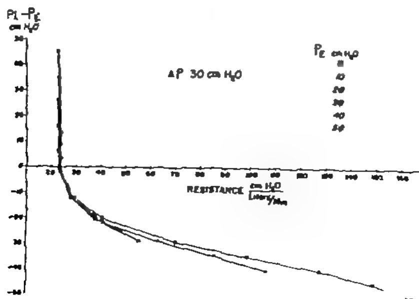


Fig 4 The data of Fig 3 are used to calculate resistance in cm. H_2O per liter per minute given in the abscissa. Transmural pressure is given in the ordinate.

mechanisms It is likely that within certain limits venoconstriction by raising the pressure in the venules which lead from collapsed capillaries can act to reduce resistance in a given vascular bed Similarly an increase in flow by raising the pressure at the venous outlet of the soft walled vessel may distend the vessel [illegible]d reduce the vascular resistance

In the present experiments lowering of the v[illegible]ous outlet lowered the intravascular [illegible] [illegible]n [illegible] transmural pressure be[illegible] [illegible]llapse occurred and re[illegible] [illegible]rkedly A similar [illegible] venous collapse and [illegible] in resistance when blood is w[illegible] from a vein at a rate more rapid than it can be supplied to the withdrawing needle [15]

Critical closing pressure Flow through some vascular bed is negligible as long as perfusing pressure is lower than a threshold static [1] or critical closing pressure It has been suggested that this is effected by muscular tone. The present data suggest that such threshold pressures may be a special case of flow through passive soft walled vessels. Thus when extravascular pressure exceeds arterial perfusion pressure soft walled segments of the vessel may collapse with the result that flow is minimal (Fig 2) As perfusing arterial pressure is elevated to a value that exceeds the extravascular pressure the vessel becomes distended and flow increases beyond this threshold value the calculated resistance falls sharply to a basal level which is not affected further by changes in either arterial perfusing or venous outlet pressure

Collapse of the tubular systems of the body by extravascular compression may account for a variety of specific clinical and physiologic effects. For example the arterial sounds of Korotkoff which result from the interactions of the pulse wave and the tendency of the cuff to collapse the artery are affected by the outlet resistance An elevated outlet pressure in the airways, as in pursed lip breathing may contribute to the distention of partially collapsed airways and in this manner reduce airflow resistance and the work of breathing

Other studies in this laboratory demonstrate similarities between the flow and resistance patterns of the kidney and lung and those of soft walled Penrose vessels. The related phenomenon of "autoregulation" may also be a special property of enclosed soft walled passive vessels.[17]

The "Starling resistance." Many physiologic experiments have utilized variable Starling resistances consisting of enclosed soft walled vessels similar to those of the present experiments. The present data which show that the resistance to flow through this device may vary greatly depending on the level of the outlet pressure suggest that some of the data obtained with the Starling resistance may require re-evaluation

Conclusion Some of the paradoxes observed in pressure/flow relationships in tubular systems of the body may reflect the degree of vascular collapse as transmural pressure passes through zero to become positive or negative

Summary

Flow through a segment of soft walled Penrose tubing was measured as perfusing head extravascular pressure, and outlet pressure were varied

As long as transmural (intravascular minus extravascular) pressure at the downstream end of the soft walled segment was positive the vessel was distended and resistance was relatively low and unaffected by inlet or outlet pressures. When transmural pressure became zero the vessel was only partially filled and delivery for a given arteriovenous pressure gradient decreased with the reduced cross section of the vessel When transmural pressure was negative a rise in venous pressure raised intraluminal pressure, and when this was sufficient to produce a positive transmural pressure the collapsible segment became distended and resistance was diminished. Further rises in transmural pressure had minimal effects on resistance. Implications of these findings in terms of critical closing pressure the Starling "resistance" and related problems of flow are discussed.

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Complete bypass of the right heart

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According to the classic concept of hemodynamics it is the pumping action of the right ventricle which is the driving force for pulmonary blood flow. Recently, enough experimental[1-11] and clinical[14] evidence has accumulated to suggest that it may be possible under certain conditions to have adequate pulmonary blood flow and normal venous pressure even in the absence of the pumping action of the right ventricle. These observations, even though very valuable, are still not adequate to prove that circulation could exist without any participation of the right ventricle. Such a proof could be obtained only by completely bypassing the right heart.

In previous studies[14-19] it has been demonstrated that *partial bypass of the right heart* could be successfully performed by anastomosing the proximal stump of the divided superior vena cava to the distal end of the similarly divided right pulmonary artery. On the other hand, efforts to *bypass the right heart completely*[20,21] have been uniformly disappointing.

The purpose of this paper is to examine the cause of the failure of these experiments and to present a method with which complete bypass of the right heart could be accomplished.

Material and methods

The experiments were performed on dogs which weighed from 10 to 25 kilograms. With endotracheal anesthesia a thoracotomy was performed in the fourth right intercostal space. The right pulmonary artery was dissected free, ligated at its origin, and divided distally to the ligature. Similarly, the superior caval vein was ligated at its junction with the right atrium and divided. Thereafter an end-to-end anastomosis was performed between the distal stumps of these two vessels.

The second stage of the procedure followed the first operation after 6 to 8 weeks. The body temperature of the animals was lowered to 29 or 30 C. by external cooling. The arterial and venous pressures, as well as the changes in temperature and the arterial oxygen saturation, were monitored. The left side of the chest was opened through the sixth intercostal space, the lower aspect of the heart, the pulmonary veins, and the inferior caval vein were exposed. The latter was divided just before it entered the right atrium, the proximal end was ligated, and the distal stump was anastomosed to the left atrium. During the occlusion of the inferior vena cava 300 c.c. of blood which contained 1 mg.

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Table I

	Pre op	Postoperative days						
		1	2	3	4	5	6	7
Mean pressure in the inferior vena cava (mm. Hg)	4	6	4	7	6	8	4	(+)

of Neo-Synephrine was transfused In the postoperative period the animals received care which was comparable to that given to patients undergoing major thoracic operations.

As a result of these procedures the entire venous drainage of the body (save the coronary circulation) bypassed the right heart. The blood from the superior caval vein flowed into the right pulmonary artery the inferior caval vein was drained into the left heart. (See Fig 1)

Results

After a number of preliminary experiments this procedure was performed on 28 dogs, of which 20 survived the second stage. An additional 4 died within 4 hours of the operation Eight of the other 16 animals lived 3 days or longer The longest survival was 7 days and 8 hours.

Most of the dogs regained consciousness in 2 to 4 hours after the second operation. They appeared ill the mucous membranes were more or less cyanotic and the respiration was rapid but they had no peripheral venous congestion With the exception of one dog which had paralysis of the hind legs, the animals had no signs of neurological damage. They were able to walk, take nourishment etc

Six of the animals underwent heart catheterization on the third postoperative day at which time the catheter passed without difficulty through the caval-atrial and caval-pulmonary anastomoses. The arterial pressure as well as the pressure in the superior and inferior caval veins were within normal limits. The arterial oxygen saturation of the animals varied between 59 and 79 per cent with an average of 72 per cent. Angiocardiography showed that the dye passed rapidly from the superior vena cava into the right lung from the inferior vena cava into the left heart and systemic arteries. (See Fig 2.) The venous pressure was monitored continuously in one animal for 6 days, and showed no significant changes (Table I)

In the final hours of life the animals showed signs of progressive anoxia rather than symptoms of heart failure. They became lethargic and refused to take any nourishment, and their dyspnea and cyanosis became progressively worse. In some of the dogs the arterial oxygen saturation fell as low as 37 per cent. Autopsy revealed that the anastomoses were open in all animals. Pleural effusion was found in 4 dogs. This was thought to be due to the recent operation rather than to heart failure. (See Fig 3)

In an additional 26 animals not included in this series an attempt was made to extend the period of survival by (a) reversing the sequence of the two operations (b) temporary cross-clamping of the descending aorta during performance of the caval-atrial anastomosis (c) doing the entire procedure in one stage (d) omitting the hypothermia (e) adding a third anastomotic operation (subclavian-pulmonary anastomosis) to the procedure None of these measures prolonged the life of the animals.

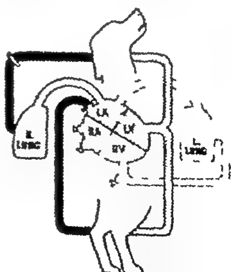


Fig 1 Schematic presentation of the circulation after superior vena cava-right pulmonary artery and inferior vena cava-left atrium anastomosis. The dotted line shows the

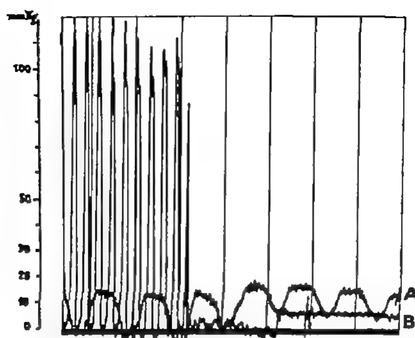


Fig 2 Measurements of blood pressure after complete bypass of the right heart. *A* Catheter withdrawal curve from the right pulmonary artery into the superior vena cava. *B* Catheter withdrawal curve from the left ventricle and left atrium into the inferior caval vein.

Discussion

The first attempt to bypass the right ventricle completely was made by Rodbard and Wagner[19] in 1949 Since then about a dozen different methods have been tried in order to accomplish this goal All of these are modifications of the following basic techniques (a) the drainage of both caval veins into the pulmonary artery or its branches[21, 22] (b) the creation of a right atrial–pulmonary artery anastomosis, with occlusion at the same time of the tricuspid and/or pulmonary orifice.[19, 20, 27]

In most cases in which these methods were experimentally or clinically applied the subject died within a few minutes. The longest survivals after the *bypass of the right ventricle* were 5 hours[23] and 2 days[24]—both were clinical cases. The maximum survival after *exclusion of the entire right heart* was reported as 164 seconds.[25]

Without going into details suffice it to say that our previous studies generally paralleled those done by the above-mentioned investigators. Analyzing the cause of the *failure of these experiments* we found that the following factors were mainly responsible

1 Overdistention of the right ventricle. Experience has shown that any procedure which occludes the right ventricular outflow tract is doomed to failure because overdistention of this chamber and cardiac standstill rapidly occur This could not be prevented by the simultaneous occlusion of the tricuspid orifice because some blood enters the right ventricle through septal pores, and if there is no route of escape, this chamber rapidly overfills.

2 Sequestration of blood in the splanchnic area. It was observed[11] that moderate elevation of the venous pressure is well tolerated in the upper part of the body However an acute increase in pressure in the inferior caval area rapidly leads to pooling of blood in the liver and splanchnic veins.[26] This might explain why superior vena cava–pulmonary artery anastomosis is tolerated well and why inferior vena cava–pulmonary artery shunts (direct or indirect) are inconsistent with compensated circulation

These considerations led us to give up the attempt to drain the inferior caval vein into the pulmonary circulation and to experiment instead with a shunt between

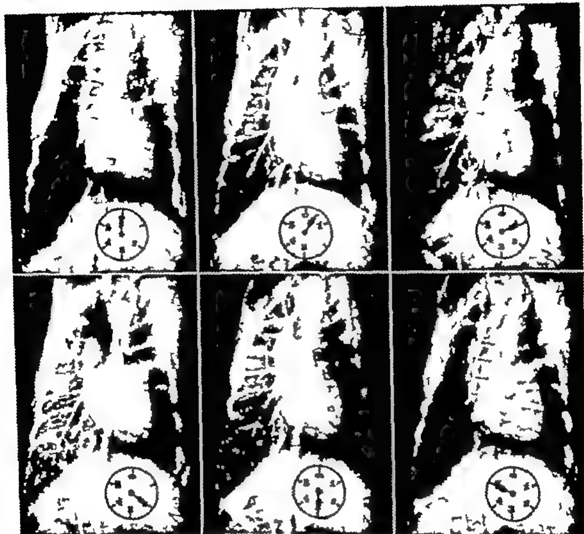


Fig. 3. Angiocardiograms after complete bypass of the right heart. The dye injected into the superior vena cava flows into the right pulmonary artery; the contrast material introduced into the inferior vena cava rapidly enters the left heart and systemic arteries. (The clock shows the time in seconds).

the inferior vena cava and the left atrium.[22,24] The feasibility of such a shunt was accidentally discovered when we had the opportunity to study a patient in whom the inferior vena cava was inadvertently transplanted into the left atrium during the repair of an atrial septal defect. Other than cyanosis and fatigability, the patient did not show any other signs of circulatory disturbance.

Through the use of a combination of caval-pulmonary and caval-atrial shunts, survival of more than 7 days has been achieved. After this length of time, however, the animals perished, probably because of chronic anoxia caused by the right-to-left shunt. In spite of this, the physiologic fact that circulation is possible without participation of the right heart is proved by these experiments; this proof was their sole aim. Eventually, by modifying our technique and improving our postoperative care, we hope that survival for more prolonged periods will be obtained.

Summary

The right ventricle is generally considered to be an organ that is indispensible to the circulation and essential in maintaining normal venous pressure and ade

quate pulmonary blood flow This concept has been recently challenged by several investigators. These observations, even though very valuable, are still not adequate to prove that circulation could exist without any participation of the right ventricle Such a proof could be obtained only by completely bypassing the right heart.

We have presented our experiments in which the right heart was completely bypassed by an anastomosis of the superior vena cava to the right pulmonary artery and transplantation of the inferior vena cava into the left atrium It is demonstrated that the entire right heart could be excluded from the circulation for a period as long as 7 days without significant changes in the arterial and venous pressure. However the concept that a compensated circulation can be maintained for more prolonged periods without any participation of the right heart still awaits further experimental and clinical proof

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Case reports

Self-sealing ventricular septal defects of the heart

Report of two cases

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Ventricular septal defects of the heart are common congenital anomalies. Many authors, on the basis of a disappearing murmur or changes in cardiac catheterization studies, have observed the spontaneous, functional closure of certain ventricular septal defects. Recently Hofman and associates during cardiac surgery in 10 patients each with pulmonic stenosis septal defect, and elevated right ventricular pressure obtained evidence in 2 that the medial leaflet of the tricuspid valve had functionally occluded a defect in the membranous portion of the ventricular septum. Hartmann[8] and Majka and associates,[9] each with an incidental autopsy finding concluded that the medial leaflet of the tricuspid valve had produced anatomic closure of a defect in the membranous portion of the ventricular septum. Lev[11] in a presentation on congenital heart lesions and in a recent symposium[12] has depicted similar heart lesions. However these latter authors have cited no independent clinical evidence which proves the former existence or patency of the proposed closed defects. Indeed Hartmann concluded that the apparent defect in his case probably closed in utero and had never been patent during extrauterine life.

Various theories attempt to explain the spontaneous closure of defects which involve either portion of the ventricular septum. For those defects which are thought clinically to be in the muscular portion of the septum the closing event is explained as either a result of lengthening and narrowing of the defect during growth of the heart[13, 4] or a result of diminution of the defect from progressive hypertrophy of the surrounding septal myocardium.

Thus far it seems that the anatomic explanation for the permanent closure of many clinically observed septal defects has been mainly speculative. It also seems that to date insufficient data have been presented to corroborate the theories on the closure of septal defects. To our knowledge no report has yet adequately correlated a given ventricular septal defect, previously diagnosed clinically with the defect's subsequent anatomic closure later proved pathologically. The purpose of this report then is to present clinical and pathologic features of 2 cases of "self sealing" ventricular septal defects in children. An attempt is made to elucidate the evolution of the total lesion and to suggest possible pathogenetic factors in the self sealing process.

Case reports

Case 1 H h., age 12 years, was premature white male inf t who was seen t The Boston Floating

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Hospital on three occasions during the year 1948. At birth, he had multiple congenital anomalies of the lower trunk and extremities, and persistent cyanosis. The heart was enlarged to percussion, and the enlargement was verified by chest x-ray examination. A loud, Grade 4 systolic murmur was present over the lower sternum and most of the precordium. An electrocardiogram was interpreted as borderline, revealing an atrial rate of 160 to 165 beats per minute slightly peaked upright P wave upright T and T_2, flat T_3, and flat T waves in Leads V_4, V and V

During the time of the second hospitalization he was treated once for bronchopneumonia and once for severe bronchitis. After the second admission he had no further heart symptoms. On the third hospital admission, however the heart was enlarged to the mid-clavicular line and he still had the systolic murmur then described as Grade 3 nontransmitting and most intense in the third left intercostal space. A repeat electrocardiogram revealed sinus tachycardia with a rate of 160 beats per minute P-R interval of 0.08 second, a normal QRS complex, and semivertical position with increased voltage. In addition, the patient had a moderate anemia, normal blood leukocyte count, and positive culture of *Streptococcus viridans* from the throat.

Next, the patient was seen at the Shriners Hospital for Crippled Children in November 1956 for an orthopedic problem. His heart and lungs were normal on chest x-ray examination, and the systolic murmur was stated to be absent.

His final hospital admission was at the Massachusetts General Hospital on July 28 1960 because of the sudden onset of dyspnea, cyanosis, stupor and marked abdominal distention all of a few hours duration. Subsequent evacuation of massive fecal impaction from the rectum gave temporary improvement Within minutes his condition worsened and he developed cardiac arrest. Attempts to revive him by open cardiac massage failed and he died 2¼ hours after admission. The presence or absence of the murmur at this time was not recorded.

The autopsy* was performed 11 hours post mortem. The body was that of a poorly developed boy which measured 130 cm in length and weighed 65 pounds. A large sacral spina bifida was associated with agenesis of the sacral spinal cord segments The viscera showed marked pulmonary congestion with minimal focal bronchopneumonia congestion of the liver and multiple foci of necrosis in the spleen and abdominal lymph nodes.

The heart weighed 200 grams and had normal contour The anterolateral aspect of the left ventricular epicardium contained focal fibrous adhesions. A few scattered subepicardial petechiae were present, probably secondary to the previous cardiac massage. A 0.6 by 0.7 cm. area of the free margin of the medial leaflet of the tricuspid valve lay firmly adherent to the adjacent interventricular septum and formed complete closure about the circumferential margins of an ovoid, 0.4 by 0.6 cm.

*Performed by Dr. Miller at the Massachusetts General Hospital, Boston, Mass.



Fig. 1. Case 1. Gross photograph of left ventricle showing the sealed defect situated just inferior to and between the right and posterior cusps of the aortic valve. The ridges which traverse the base of the defect are the chordae tendineae of the medial leaflet of the tricuspid valve.



Fig. 2. Case 1. Gross photograph of right ventricle showing the area of fibrous adherence of the medial leaflet of the tricuspid valve to the ventricular septum.



Fig. 3. Case 2. Gross photograph of left ventricle. The defect is larger and somewhat lower than the defect in Case 1.

defect in the membranous portion of the septum (Figs. 1 and 2). The papillary muscle and chordae tendineae of this leaflet were shortened, flattened, thickened, and fused to the septum just inferior to the defect. The remaining heart valves and structures were normal grossly. The chambers contained no mural thrombi.

Microscopically, the myocardium was normal throughout. The scarring about the tricuspid leaflet and contiguous defect margins was nonspecific and gave no clues as to its cause of origin.

Case 2. P.L.C., age [illegible] years, was a premature Negro female infant who was born at the Louisville General Hospital on Dec. 18, 1946, with obvious Mongoloid features. T years later a systolic murmur was detected which was described as harsh, Grade 3, and heard over the entire precordium. Chest x-ray and fluoroscopic examinations revealed bilateral pulmonary edema and congestion, pneumonitis, and generalized cardiomegaly with "mitral configuration." The electrocardiogram was interpreted as "probable normal" and revealed regular

sinus rhythm, rate of 106 beats per minute, and diphasic T waves in Leads CF and CF_4.

The patient was seen numerous times up to the year 1955 for episodes of acute tonsillitis, acute tracheobronchitis, and pneumonia, all principally treated with penicillin. During her admission to hospital on July 17 1950 the heart as still noted to be enlarged and the murmur was further de scribed as Grade 3 early systolic over the entire precordium, with maximal intensity in the third and fourth intercostal spaces along the left sternal border with some transmission toward the base, and pansystolic over the aortic area. By this time, the patient was quite mentally retarded.

I 1955 her heart was normal in size to percussion and chest x-ray examination. The systolic murmur was still present. The electrocardiogram was interpreted as normal and revealed sinus tachycardia ith rate of 122 beats per minute a P R interval of 0.16 second and a QRS interval of 0 05 second.

The patient systolic murmur persisted uncor rected until 1957 at which time her heart was re ported to be normal on physical examination. Thereafter no further mention of the presence or bsence of the murmur is recorded.

She entered the hospital for the final time on March 12 1962, for observation because of the sudden onset of nausea, vomiting, headache fever and epigastric pain all of few hours duration. There was blood leukocyte count of 21,800 per cubic millimeter with 92 per cent polymorphonuclear leukocytes, 6 per cent lymphocytes, and 2 per cent monocytes. X-ray examination of the abdomen and chest as interpreted as showing no intestinal cardiac, or pulmonary abnormalities. A few hours later she was discharged on chloramphenicol medica tion with a diagnosis of acute gastroenteritis. The following day she died suddenly at home

The autopsy* was performed 3½ hours post mortem. The body was that of an obese Negro girl hich measured 146 cm. in length. The viscera re vealed disseminated focal, acute inflammation. The heart weighed 230 grams and showed mild prominence and hypertrophy of the right chambers. The pericardial space contained 150 c.c. of clear yellow fluid. The epicardium contained scattered, fibrous adhesions. The medial leaflet of the tricuspid valve was fibrously adherent to the interventricular septum, mostly the membranous portion, and formed base bout the margins of a high ventricular septal defect. This leaflet closure had the configura tion of small aneurysmal sac which bulged slightly into the right ventricular cavity (Figs. 3 and 4). The defect measured 1.5 by 2.0 cm. and was ovoid. The right entricular endocardium opposite the septum, contained 1.5 by 2.5 cm. whitish plaque. The mitral valve showed a slightly thickened anterior leaflet and single 2 mm. errucous nodule on the free margin of the posterior leaflet. There ere no mural thrombi noted.

Microscopically the scarred areas suggested only healed, nonspecific process of the mitral valv the tricuspid leaflet, the septal endocardium, and the pericardium. In addition the myocardium of both entricles showed subacute, nonspecific myo-

*Performed by Dr Kavachevich at the Louisville General Hospital Louisville, K

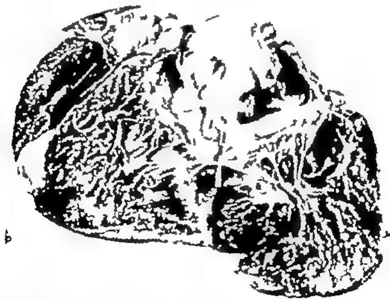


Fig 4 Case 2 Gross photograph of right entricle showing again an area of fibrous adherence of the medial leaflet of the tricuspid valve to the entricular septum. This area projects into the ight entricular cavity as small aneurysmal sac. Note the jet lesion of the right ventricular endocardium (partially hidden by the anterior leaflet of the tricuspid valv).

carditis with many eosinophils possibly a reflection of septicemia or an allergic myocarditis. Definite rheumatic nodules could not be identified. As in Case 1 the fibrosis which involved the medial leaflet of the tricuspid valve and the ventricular septum appeared to be secondary to healed, nonspecific endocarditis. The circumscribed plaque of endocardial fibrosis of the lateral right ventricular wall was interpreted as a jet lesion secondary to the previous left-to-right shunt of blood through the defect.

Each of these patients died of an acute fulminating illness. The autopsy results suggest systemic infections as the probable causes of death. Blood and lung cultures taken post mortem in each case, failed to grow any pathogens. However the second patient had received chloramphenicol just prior to death. Careful review of the clinical histories failed to reveal any known episode of bacterial or other endocarditis.

Discussion

The antemortem diagnosis of these two ventricular septal defects rests mainly on the auscultatory findings. Unfortunately cardiac catheterization or angiocardiographic data are *not* available. The clinical data further suggest that neither defect was associated with any physiologic heart block[11] or evidence of tricuspid valvular insufficiency.

Detailed evaluation of the hearts described herein revealed that the total lesion was as previously surmised[11] an ordinary congenital septal defect which became completely occluded by the fibrous adherence of the medial leaflet of the tricuspid valve to the margins of the defect.

The precise cause of this self-sealing process can only be surmised at present. From available data, three possible causes can be mentioned: (a) hemodynamic stress, (b) rheumatic or other noninfectious endocarditis, and (c) bacterial or other infectious endocarditis. In regard to the latter suggestion, the likely possibility that a bacterial endocarditis could adhere the tricuspid leaflet to the ventricular septum is further supported by a case depicted by Edwards[4] in which the posterior leaflet of the mitral valve became permanently adherent to the left ventricular wall after a *Streptococcus mitis* endocarditis.

In conclusion, the anatomic, self-sealing closure of these two ventricular septal defects occurred after birth secondary to some form of endocarditis. Presently the definitive cause (or causes) of the endocarditis is obscure.

Summary

Two cases of self-sealing ventricular septal defects in children have been presented. The clinical and pathologic data indicate that each closure was produced by the fibrous adherence of the medial leaflet of the tricuspid valve to the ventricular septum and had occurred as an acquired condition after birth. The pathogenesis of the self-sealing process is discussed briefly. The data of these cases now provide one confirmed anatomic basis for the explanation of the spontaneous closure of some high ventricular septal defects.

The authors are indebted to Dr. William M. Christopherson and Dr. Benjamin Castleman for their permission to publish these cases.

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Countershock conversion of digitalis-associated paroxysmal atrial tachycardia with block

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In the case of a patient who is receiving digitalis and suffering from congestive heart failure with an ectopic tachycardia, it is frequently difficult to determine whether he should receive more digitalis because of uncontrolled heart failure or whether the tachycardia is the result of excessive digitalization. The following is a report of such a case in which the problem was solved by the use of DC synchronized countershock.[1] In addition, this case represents, to our knowledge, the first instance in which paroxysmal atrial tachycardia with block (herein referred to as PAT with block), presumed to be due to overdigitalization and/or depletion of potassium, was converted to sinus rhythm by such countershock. In previous instances, both external AC countershock and DC synchronized countershock have been successfully employed in the management of ventricular tachycardia, atrial fibrillation, and isolated cases of atrial flutter, nodal tachycardia, and double tachycardia.[1-4] However, we were uncertain whether PAT with block, an arrhythmia commonly attributed to overdigitalization, would also respond to this form of therapy after other measures had proved to be ineffective.

Case report

A 58-year-old married white man was admitted to The Mount Sinai Hospital on Nov. 20, 1962, with the chief complaint of palpitation for 5 days. A systolic murmur had been detected when he was 17 years old. For 5 years before this hospitalization he had been treated with digitalis and diuretics for symptoms of mild cardiac decompensation. His illness was attributed to rheumatic heart disease with predominant mitral regurgitation. On Oct. 28, 1962, he was admitted to another hospital with symptoms and signs of acute pulmonary edema, probably induced by excessive ingestion of salt. An electrocardiogram was interpreted as showing sinus tachycardia and changes compatible with left ventricular hypertrophy and digitalis effect. He was treated with digoxin, mercurial injections, thiazide derivatives, restriction of salt, and bed rest, but no potassium supplements. In association with profuse diuresis, there was a 12-pound loss of weight, and marked alleviation of his symptoms. In the second week of the hospitalization he developed persistent diarrhea subsequent to the administration of laxatives. There was normal sinus rhythm at 85 to 90 per minute throughout the latter portion of the hospitalization. The patient was discharged from

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the hospital on Nov. 10, 1962, and was placed on regimen which included digitoxin, 0.1 mg. and 0.2 mg. on alternate days, together with chlorothiazide 0.5 and 1.0 Gm. on alternate days.

At home he remained confined to rest in bed because of protracted weakness. On Nov. 15, 1962, he experienced distressing palpitation. He telephoned his physician, who advised him to discontinue digitoxin and to add potassium chloride 0.6 Gm. four times daily to the regimen. Administration of chlorothiazide was not interrupted. The palpitation persisted and was attended by increasing dyspnea and orthopnea. He was given 0.25 mg. of digoxin orally and was admitted to The Mount Sinai Hospital.

Physical examination revealed a well-developed, pallid, middle-aged white man who was moderately dyspneic and who was coughing intermittently. The blood pressure was 130/100 mm. Hg, the pulse was feeble at 190 per minute, the respirations were 30 per minute, and the rectal temperature was 101°F. The cervical veins were distended with the patient reclining at 45 degrees. Râles were heard at the bases of both lungs. The heart was enlarged to the anterior axillary line in the sixth left intercostal space. The rhythm was regular. The heart tones were of poor character. A blowing Grade 2 holosystolic murmur was heard at the apex of the heart. The liver extended 2 to 3 cm. below the right costal margin. There was no peripheral edema.

Laboratory data on admission included hemoglobin of 13.9 Gm. and white blood cell count of 10,000 with slight polymorphonuclear leukocytosis. Urinalysis revealed 1+ proteinuria. The fasting blood sugar was 136, blood urea nitrogen 35, SGOT 56 units per milliliter, and ESR 15 mm. per hour. The serum potassium was 4.6 mEq. per liter. Roentgenographic examination of the chest revealed moderate cardiac enlargement with engorgement of the pulmonary vasculature and minimal obliteration of the left costophrenic sinus due to a small effusion. An electrocardiogram revealed paroxysmal atrial tachycardia at 200 per minute (Fig. 1). Massage of the right carotid sinus produced a brief run of regular blocked P waves at the rate of 200 per minute with isolated, idioventricular or irregularly conducted QRS complexes, followed by PAT with varying block. At first the block was 2:1, then of the Wenckebach type, ultimately with restoration of 1:1 response was noted.

The patient was given potassium Triplex, 10 (30 milliequivalents of potassium), by mouth and sedation with parenteral phenobarbital. Parenteral penicillin was also begun because of the presence of fever which together with the râles, suggested the possibility of an underlying pneumonitis.

The patient became increasingly dyspneic during the evening of the day of admission and was given meralluride 2 c.c. intramuscularly at 2 A.M. on Nov. 21, 1962. There was no significant clinical or diuretic response and he lost only 1 pound of weight in the next 24 hours. An electrocardiogram at 10 A.M. revealed PAT with Wenckebach phenomenon; the atrial rate was 166 per minute and the ventricular response averaged 140. Because of increasing heart failure, the patient was given 0.5 mg. of digoxin orally. By midafternoon, there was persistent PAT with 2:1 block; the atrial rate was 188, and the ventricular rate was 94 per minute. Potassium chloride, 6.0 Gm. (80 milliequivalents), was administered intravenously over a period of 18 hours without effect. At 7:15 P.M. on November 22 an electrocardiogram revealed PAT with 1:1 conduction at 204 per minute. This persisted, and, because increasing cardiac decompensation ensued, he was given additional digoxin, 0.5 mg. orally, at 8 P.M. At 10:30 P.M. PAT with 1:1 conduction at 215 per minute was recorded. The patient's clinical condition continued to deteriorate, and he was rapidly approaching the development of frank pulmonary edema. But the rhythm then reverted to PAT with Wenckebach block, and shortly thereafter PAT with 2:1 block. With the slowing of the ventricular rate to 107 per minute, prompt regression of the congestive symptoms ensued.

Because of the belief that the PAT with block was due to excessive digitalis and depletion of potassium, the decision was made to administer potassium again in full dosage, and 100 milliequivalents were infused intravenously over a period of 7 hours. The atrial rate slowed from 215 to 140 per minute, but the 2:1 block persisted. In addition, hyperkalemic T waves were noted. The trial was abandoned when marked hypotension developed, and it was necessary to administer metaraminol by continuous intravenous infusion. A transient rise in blood pressure to 210 mm. Hg, while the rate of flow was being adjusted, failed to control the arrhythmia, as often occurs in paroxysmal supraventricular tachycardia without block.

Since an apparently adequate trial of potassium therapy had been given, and since it was feared to give procaine amide because of the hypotension,

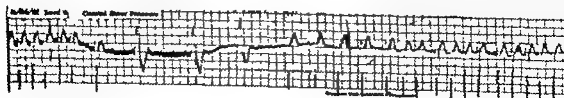


Fig. 1. Paroxysmal atrial tachycardia (PAT). Carotid sinus pressure. Run of blocked P waves with three idioventricular beats, then PAT with 2:1 block, followed by PAT with Wenckebach phenomenon, and finally PAT with 1:1 conduction.

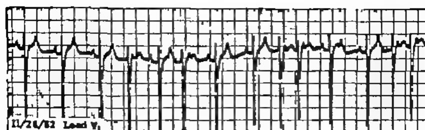


Fig. 2. PAT with block (2:1 and Wenckebach).

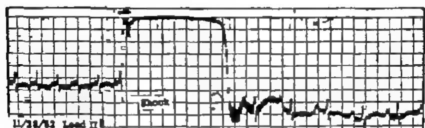


Fig. 3. PAT with 1:1 conduction. Countershock artifact followed by sinus rhythm within an interval of 2 seconds.

the decision was made to withhold digitalis and diuretics for as long as possible in order to permit gradual renal excretion to correct any overdigitalization. On November 26, PAT with 2:1 block alternating with PAT with Wenckebach persisted (Fig. 2), but by November 27 the rhythm had become chiefly PAT with 1:1 conduction at 215 per minute, and increasing congestive heart failure had become alarmingly intense. Since the hypotension had been controlled in the interim, he was now given 1,250 mg. of procaine amide intravenously over a period of 15 minutes, with constant monitoring of blood pressure and the electrocardiogram. Levarterenol had to be administered toward the end of the infusion because of resultant hypotension. Despite QRS widening from 0.08 to 0.17 second, the PAT slowed only to 130 per minute and 1:1 conduction persisted. Procaine-amide therapy was abandoned at this point, but the patient remained hypotensive throughout the next 24 hours; the blood pressure could not be maintained without levarterenol. On November 28, the patient appeared to be virtually moribund. Since his critical state appeared to allow no further delay, he was taken to the operating room while the infusion of levarterenol was continuing. Blood pressure was thus controlled despite intravenous Pentothal anesthesia and DC synchronized countershock (100 watt-second, 20-millisecond delay from peak of R wave*) was applied. Conversion to sinus rhythm at 100 per minute was thereby effected within 2 seconds (Fig. 3). When the patient recovered from anesthesia a few minutes later, he was noted to be remarkably improved; his dyspnea had disappeared and his mental state had changed from one of pronounced apprehension to that of marked euphoria. He was returned to the ward and the infusion of levarterenol was discontinued. The blood pressure remained stable at 120/80 mm. Hg. He was given one dose of quinidine 0.5 Gm. parenterally, followed by quinidine sulfate 0.4 Gm. four times daily orally. Continued improvement of his cardiac decompensation was noted and sinus rhythm persisted. Because of the persistence of symptoms of mild congestive heart failure, he was redigitalized, commencing Dec. 8, 1962, without difficulty. He has remained in sinus rhythm to this date (Feb. 19, 1963).

*The 20-msec. delay, the shortest delay possible with this device, was selected to avoid the vulnerable period within the T wave, when there is danger of inducing ventricular fibrillation. The atrial vulnerable period in which the shock might have fallen was considered to be of lesser importance.

Discussion

Although PAT with block is generally regarded as a manifestation of digitalis toxicity, the patient was given additional digitalis after the arrhythmia first appeared and soon after hospitalization. This was justified on the basis that previous digitalis dosage had not been excessive and that cases of PAT with block not due to overdigitalization had been reported.[3] Additional digitalis was considered to be indicated in order to combat progressive heart failure by increasing the degree of atrioventricular block and thus slowing the excessively rapid ventricular rate. On the other hand, PAT with block due to digitalis often occurs without an increase in dosage

when body potassium is depleted. In Lown's series, 60 per cent of the cases of PAT with block due to digitalis were precipitated by loss of potassium. The normal serum potassium in our patient was in keeping with the infrequency of decreased values of serum potassium in cases of this type. Available data suggest that either diminished myocardial potassium or potassium gradient across the cell membrane may be the important factor rather than serum potassium per se.

In our patient the history suggested both a slight increase in digitalis dosage during the previous hospitalization and a loss of large amounts of potassium. A profuse rapid diuresis with a 12 pound loss of weight had occurred in little more than a week. Anorexia due in part to severe restriction of sodium and diarrhea, due to frequent administration of laxatives during the second week of the previous hospitalization intensified the negative potassium balance.

Because of these considerations, digitalis and diuretics were discontinued after the first few days of hospitalization for the arrhythmia. Two courses of intravenous potassium therapy to the point of toxicity failed to terminate the tachycardia. The use of procaine amide likewise proved to be unsuccessful despite high dosage sufficient to produce marked QRS widening and hypotension. Lown and associates reported that PAT with block responded to potassium therapy in 23 of 25 cases and that procaine amide was also an effective agent in the treatment of this arrhythmia.

The failure of our patient to respond to these measures which are usually effective in cases of PAT with block caused by digitalis and loss of potassium posed a therapeutic dilemma. The usual role of digitalis in producing the arrhythmia, the history of digitalis therapy and depletion of potassium in our patient, and the high mortality reported if digitalis is continued were responsible for resistance to additional digitalis therapy. The intravenous administration of the rapidly acting and rapidly excreted acetyl strophanthidin has been recommended to distinguish between digitalis intoxication and the need for additional digitalis in cardiac arrhythmias but serious reactions have been reported after its use. Nor could further delay be tolerated in the hope that gradually the slowly excreted digitoxin would be eliminated and that the arrhythmia might then subside.

The combination of an extremely serious and deteriorating clinical state and failure of response to the usually effective agents despite their use to the point of toxicity appeared to provide sufficient indication for a trial of external DC synchronized countershock. Only a sudden restoration of sinus rhythm appeared to be capable of reversing the apparently hopeless clinical condition of the patient. Although the intravenous Pentothal used for the anesthesia has a hypotensive effect, it presented no new problem but intravenous levarterenol therapy was maintained throughout the brief period of anesthesia and for a period of 15 minutes thereafter. After a single shock, sinus rhythm was promptly restored.

The effectiveness of countershock in this case and the persistence of sinus rhythm thereafter is not helpful in determining the cause of PAT with block in this patient. But because of the frequent relationship of digitalis to this arrhythmia and the possible hazard in its employment, even though potassium therapy or procaine amide are ineffective synchronized DC countershock may prove to be the therapeutic method of choice under such circumstances.

Summary

The first successful conversion of paroxysmal atrial tachycardia (PAT) with block by means of external countershock is reported. The arrhythmia occurred while the patient was receiving digitalis and after the loss of potassium due to brisk diuresis and other factors and digitalis intoxication appeared to be likely. The arrhythmia proved to be refractory to intravenous potassium and procaine amide carried to toxicity but was promptly converted to sinus rhythm with a single DC synchronized countershock.

This method is suggested in the management of PAT with block when there is a dilemma whether this arrhythmia was caused by digitalis or whether further digitalis administration is indicated after conventional methods of treatment have proved to be ineffective.

We are indebted to Dr. Henry Rendell for granting us permission to report this case.

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Clinical abstract

A 39-year-old man, a cable hauler, was admitted to the hospital for investigation of ankle edema which had been present for 2 months, and increasing shortness of breath.

He had been perfectly well until 4½ months prior to admission, when, according to his doctor, he had suffered an infection of the respiratory tract, associated with cough and the appearance of streaks of blood in his sputa on several occasions. During this illness he had an attack of severe pain in the left side of the chest, exacerbated by deep inspiration. This lasted for 10 days, waxing and waning in intensity. The doctor diagnosed the illness as viral bronchitis, prescribed a cough suppressant, and advised him to stay in bed. He seemed to make a good recovery and returned to his work, which was fairly heavy.

Two months later he suffered another almost identical illness which was treated in the same manner. It was after this that he first noticed the swelling of the ankles and the increasing shortness of breath. The doctor now prescribed a diuretic drug, with some benefit. He was soon able to return to work, but breathlessness severely limited his activity.

Previous history. At the age of 12 years he had had an illness which was diagnosed as rheumatic fever and was kept in bed for some months. This illness did not seem to damage his heart, and after-ward he led a very active life. He served in the Army during the Second World War and when discharged in 1946 he was medically graded A1. In 1953, he underwent a thorough medical examination for superannuation purposes, and no abnormality was detected. He smoked 10 to 12 cigarettes daily and drank no alcohol. There was no significant family history.

Hospital admission. At the time he was admitted to the hospital his breathing was moderately distressed and there were obvious signs of congestive heart failure: the jugular veins were dilated 5 cm. above the root of the neck and the edge of the liver was palpable 3 cm. below the right costal margin. His legs were swollen. It was noted that his complexion was reddish-brown, and this was attributed to his outdoor life. The heart was described as being slightly enlarged, but the position of the apex was not recorded. A friction rub was said to be audible loudest over the apex but within 48 hours it was noted that this had been replaced by a mitral systolic murmur. His blood pressure was 125/90 mm. Hg.

A provisional diagnosis of diffuse myocardial disease was made, and treatment was begun with digoxin and a diuretic drug. There was rapid improvement in the symptoms, although frequent ventricular extrasystoles now began to occur and persisted despite a reduction in the dose of digoxin.

Laboratory investigations. A number of investigations were made. The hemoglobin value of the blood was 15 Gm. per 100 ml. The red corpuscles appeared

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Fig. 1. X-ray film of the chest made 1 week after the patient was admitted to the hospital.

t be normal and the platelets were plentiful. The leukocytes numbered 9,800 per cubic millimeter and were in normal proportions. The erythrocyte sedimentation rate was near the lower limit of the normal. No lupus erythematosus cells could be found in the venous blood—four examinations were made. The antistreptolysin titer was normal. The levels of sodium, potassium, and bicarbonate in the plasma were normal. The blood urea level was 35 mg. and the serum cholesterol level was 190 mg. per 100 ml. The serum bilirubin level was 1.2 mg. per 100 ml., but after a week or so it was normal. The Rose-Waaler test was reported to be positive, but 2 weeks later it was negative. The serum protein levels were normal and so were the flocculation tests. The serum alkaline phosphatase level was 16 King-Armstrong units. The fasting blood sugar level was 140 mg. per 100 ml.; after the ingestion of 50 mg. of glucose the level rose to 310 mg. in 1½ hours and had fallen to 200 mg. in 2 hours. The serum iron level was normal. Agglutination tests of the serum against cultures of *Salmonella typh*, *Brucella abortus*, and *Proteus* OXK and OX19 were negative. The Eagle flocculation test for syphilis was negative. Blood cultures grew no microbes. The serum glutamic oxalate transaminase test showed a level of 50 units per 100 ml.

Microscopy of the urine showed no cells or casts, and no microbes grew on culture. No hemosiderin was found in the urine, and no abnormal pigment was found on biopsy of the gum, liver, and skin. The intracutaneous tuberculin (Mantoux) test yielded reaction. The radioactive-iodine-uptake test showed no deficient or excessive activity of the thyroid gland.

X-ray examination. X-ray examination of the chest showed slight enlargement of the heart (Fig. 1), and there was a suggestion of pulmonary edema at one stage. Valve tomography failed to demonstrate any calcification.

Electrocardiography. The electrocardiograms were said to show ischemia of the heart (Fig. 2), and after the patient had been treated with digoxin frequent ventricular extrasystoles were recorded.

At the conclusion of all these investigations no definite diagnosis had been established, and the condition of the patient was static. Four weeks after his admission to the hospital steroid therapy was tried. This made no obvious difference, though his requirement of diuretic increased.

Seven weeks after his admission, when he was feeling quite well, he suddenly collapsed and died.

Discussion

DR. EPPS: In approaching this problem I would like to mention first several conditions which I believe are unlikely to constitute the diagnosis, but which should have some place in our discussion. I will then pass on to the more likely possibilities.

Congenital heart disease is unlikely here because there seems to be no evidence of malformation of the heart. It is unlikely that there has been any abnormality in this man from birth, with perhaps one exception—fibroelastosis. That is an occasional cause of persistent cardiac failure in children, but it is rather rare at this age.

Coronary artery disease has always to be considered in a patient of this age because it is so common and can occasionally present with persistent heart failure and remain unrecognized. We have nothing in the history here to suggest coronary artery disease. I notice that the serum cholesterol level was normal. That is perhaps not of very much value in excluding this disease, but it is a pointer. The ECG would certainly be consistent, but we have no evidence in these tracings, and there were a number recorded, of cardiac infarction—and that, I think, would be a necessary sequel to explain this man's termination. In all, the picture is unlike that of coronary artery disease.

In passing we should mention pulmonary heart disease. We have to think of the possibility of repeated pulmonary embolism or pulmonary infarction or thrombosis of the pulmonary arteries leading to right-sided heart failure and death. This suggestion is raised by the fact that the patient had pain of a pleuritic nature in the chest and coughed up blood-stained sputum

on two occasions prior to his admission to the hospital. I think that we can reasonably exclude this possibility. There is no evidence of chronic pulmonary disease. In the ECG there is no suggestion of right ventricular hypertrophy. There are no abnormal P waves which one might expect to find if this patient were suffering from right ventricular strain due to interference with the pulmonary circulation.

I must mention constrictive pericarditis. That must always be considered in an obscure case of congestive failure. In this man's case the history is quite unlike that of constrictive pericarditis in that it was of short duration. The congestive failure was of sudden onset, not gradual as is usually the case in constrictive pericarditis. Also the clinical findings were unlike those of constrictive pericarditis. No calcification in the pericardium was noted on the x-ray films and no very loud third heart sound was audible over the precordium.

I would like to pass on after that to a discussion of myocarditis. Firstly, rheumatic carditis should be carefully considered. In the case of rheumatic carditis we might expect a previous history of sore throat prior to the first episode of chest pain, and we might reasonably expect to find some history at least of pain in the joints during the 4 or 5 months of the illness. These were not noted. Furthermore the sedimentation rate remained low throughout the course of the illness, probably low because of the congestive cardiac failure, and the antistreptolysin titer was normal. The patient was said to have a friction rub, presumably a pericardial friction rub, after admission; this rub was said to have lasted only a short time, and a systolic murmur at the apex was noted after this. These findings do raise the possibility of rheumatic carditis, but I think that we have nothing else to support this suggestion.

Then we have to consider the other causes of myocarditis, and there are many. I will pick out the most likely ones and leave the others to save time. First of all bacterial infections—diphtheria, pneumonia, and such—occasionally lead to carditis. We have no evidence of any infection of a grave nature leading to this congestive failure. There is a possibility on the history that he had an infection in the chest, probably bronchitis, 4½ months before admission, but it seems unlikely that he had pneumonia. I understand that no x-ray film was made at that time. Other infections which cause myocarditis are viral infections such as mumps. There are rarer causes, parasitic and fungus infestations, but I do not believe that in this man we are dealing with any of these conditions. In passing one might mention toxoplasmosis. In that condition glandular enlargement is very frequent, but it was not noted here.

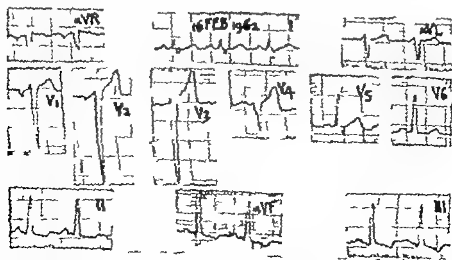


Fig. 1. Electrocardiogram recorded when the patient was admitted to the

The muscular dystrophies are occasionally associated with progressive cardiac failure There was no evidence in this man of a muscular dystrophy and I think, no evidence to suggest that he had a tumor of the heart which is another cause of progressive irreversible congestive heart failure

Then we have to consider the endocrine disorders—thyroid disorders, myxedema thyrotoxicosis. We have no clinical evidence of these and the radioactive-iodine-uptake test was normal Reactions to drugs occasionally lead to persistent myocarditis with failure—drugs such as emetine and quinidine. There is no evidence of exposure to any drugs prior to his first illness so that this seems to be an unlikely explanation

Collagen diseases we have to consider rather more closely Scleroderma and dermatomyositis may involve the heart and require consideration These conditions give rise to manifestations in skin and muscle which were not present in this patient Skin biopsy was carried out with a negative result and this is perhaps the most reliable investigation in arriving at a diagnosis of this type of collagen disease I the case of periarteritis nodosa involving the heart I think that the situation is similar for here we have none of the other features of the disease. There has been no evidence of renal damage or hypertension no note of any nodules found on peripheral arteries no presentation with bronchial asthma none of the clinical features that one might look for Disseminated lupus erythematosus requires rather more careful consideration. I note from the investigations that this was carefully sought for lupus erythematosus cells were looked for on no less than four occasions. The sex of the patient is wrong for disseminated lupus in that 90 to 95 per cent of all cases occur in women usually in the younger age group although occasionally it is seen in a man The complete absence of pain in the joints fever and rash are points against this diagnosis. The main points that one would consider in favor apart from congestive failure were the note that he had a pericardial friction rub on admission a cardiac murmur after this which was very nonspecific and pleuritic chest pain on two occasions before admission On the negative side are the absence of anemia and splenomegaly I think that in all especially in view of the failure to find lupus erythematosus cells in the blood we can reasonably discard this diagnosis also.

We should consider rheumatoid arthritis. Rheumatoid arthritis may affect the heart and cause congestive failure in one of several ways. It may cause myocarditis or a valvular lesion not unlike those of rheumatic fever which may lead to congestive failure. This man had no clinical evidence of rheumatoid arthritis. There was no mention of pain in the joints at any stage It is interesting that the Rose-Waaler test (the sheep-cell test) was positive on one occasion and negative 2 weeks later This test is said to be positive in 70 to 80 per cent of the patients with rheumatoid arthritis but there are many patients who have false positive tests and there are a proportion who show a negative result and still have rheumatoid arthritis. I have noticed positive results in many other conditions including disseminated lupus erythematosus and amyloidosis and I think that we must allow very little importance to one positive result with this test. I think that we may reasonably discard rheumatoid arthritis.

The metabolic and nutritional disorders also require careful consideration There is no history of an excessive use of alcohol in this patient and I think that that can reasonably be ruled out.

Amyloidosis must be considered Primary amyloid disease of the heart occurs almost exclusively in an age group older than this man's. He was 39 and it is uncommon indeed to see the disease before the age of 45 That is the only real objection that I can offer to this diagnosis but I think that it is a valid one

Diabetes mellitus was found in this man and the diagnosis was confirmed by the glucose tolerance test. Can diabetes mellitus cause congestive failure in this way? Well only indirectly can it cause cardiac manifestations and without complications it cannot reasonably be considered to be a cause of this kind of progressive and fatal congestive failure So I think that diabetes mellitus alone without complications such as coronary artery disease can be excluded

Beriberi is excluded by the history. There is no actual note of the diet here but we are told that he was not a heavy drinker and that he took a normal diet.

Hemochromatosis should be discussed I think. This was, I should imagine, the clinical diagnosis when this patient was admitted to the hospital—or following the first bracket of investigations. The points in favor of hemochromatosis are clinical and are very impressive. The patient had diabetes mellitus, and he had progressive congestive failure and some evidence perhaps of hepatic involvement. The serum alkaline phosphatase was slightly above normal and so was the serum glutamic oxalacetic transaminase. These findings could result from persistent congestive cardiac failure with hepatic congestion. But at the same time it is very common to find liver function tests giving normal results in the presence of congestion of the liver of several months duration. I think that there is slight evidence here to favor some disorder of the liver apart from chronic venous congestion. The liver was enlarged and showed abnormal function tests as well. There is the suggestion that the patient may have been pigmented although the reddish-brown complexion was attributed to the sun. These are the main points in favor of a diagnosis of hemochromatosis. The points against it are quite formidable—the normal serum iron values and the normal biopsy results. However I believe that we are not entitled to discard the diagnosis on the basis of these findings.

Lastly I would like to mention isolated myocarditis, which is a diagnosis by exclusion—an uncommon and not very satisfactory one. It is possible that this patient may come into this category but I think that we should not readily resort to this last diagnosis.

Considering every aspect of the clinical features in this patient I would choose a diagnosis of hemochromatosis with primary cardiac involvement some involvement of the liver and no deposition of iron in appreciable quantity in the skin or in the gums.

One or two points perhaps require elaboration such as the presentation of the illness. I suggest that this patient did not suffer initially and primarily from an infection in the chest but from pulmonary infarction which was a complication of congestive failure at the commencement of his illness that he improved and remained well until the second episode 2 months before his admission to the hospital and that then perhaps the same thing happened again. I shall be interested to know later whether any trace of this was found.

There are several other points of interest. One is the chest x-ray film which is said to have shown slight cardiac enlargement. This is unusual in a fatal myocarditis. Cardiac enlargement is usually moderate or gross. When it is slight it raises the possibility of such conditions as constrictive pericarditis but actually the second film shows a quite large heart it is at least moderately enlarged.

The electrocardiograms show T wave abnormalities in the left ventricular and posterior leads. This is a frequent finding in myocarditis from many causes and is nonspecific. Frequent ventricular extrasystoles appeared during the patient's stay in the hospital. This when it occurs without previous record of extrasystoles, is suggestive of myocardial disease. I think that this lends some support to the general statement that we are dealing with a progressive myocarditis but it helps us not at all in deciding the particular cause. I think that that is all I have to say.

MODERATOR: Thank you Dr Epps. You seem to have excluded every disease in the calendar—except hemochromatosis. You cannot quite dispose of that.

DR. EPPS: That is so.

DR. KRAUS: This case reminds me of that of the young woman which was presented here about 2 years ago. There were signs of myocardial disease, pericardial disease and endocardial disease. I suggested that it might be pancarditis but it was found to be a tumor of the heart. Perhaps this may be such a case.

MODERATOR: Yes indeed Dr Kraus. That might explain the pericardial friction and the extrasystoles might it not?

DR. VINCENT: The mode of death which seems to have been a puzzle brings two possibilities to mind. One is the possibility of a ball valve obstruction of the cardiac

outflow brought about suddenly by a myxoma or something similar The other possibility is that all along there was evidence of a conduction defect—if one sees ventricular ectopic beats as conduction interference rather than as myocardial disease. This if it were spreading might have led to sudden death

MODERATOR I do not quite follow

DR VINCENT Then again I wonder whether any other condition existed similar to that produced by hemochromatosis, due not to the deposition of iron but to the deposition of some other rarer metal

MODERATOR What an interesting suggestion! Are there any others? Surely there are others.

Well I notice that we have only one record of the serum electrolyte levels. What do you think of this notion—that all the digoxin and diuretic administration may have leached potassium from the system, and that that may have accounted for the heartbeat becoming irregular and remaining so The heart that is stimulated to frequent ventricular extrasystoles may be stimulated to ventricular fibrillation may it not? I wonder what effect the steroid therapy may have had on the heart

Tell us Dr Isbister—this patient was under your care I believe—why was treatment begun with a diuretic drug in addition to digoxin? Also I wonder whether you would care to tell us, without for the present revealing the diagnosis if that is possible what was the reason for the steroid therapy a little later on? We are told that the blood sedimentation rate was at the lower level of normal If the blood sedimentation rate is low could there be present any collagen or other disease likely to respond to steroid therapy?

DR. ISBISTER In regard to the use of digitalis and a diuretic which if my memory is correct was mersalyl I do not think that there was anything unusual about that. I know that either one alone works quite well in heart failure but this man had quite severe congestive heart failure and our belief was that we should give him the benefit of this double therapy In regard to steroids at that particular stage we were unable to make a definite diagnosis. The patient had been in the hospital for 2 or 3 weeks and although his heart failure had improved a little we thought that we were not getting very far He had had rheumatic fever at the age of 12 and we considered that he may have been suffering from a reactivation of rheumatic carditis. If that were so steroid treatment might have been of great benefit to him and we believed that it was desirable to give him that benefit. But as was mentioned it gave no benefit whatever and it was subsequently stopped

Now if I might just comment on a couple of things. I think that Dr Epps is quite right in suggesting that the most likely clinical diagnosis is hemochromatosis. This man was pigmented he had hyperglycemia and he had an enlarged liver Clinically that is sufficient to make a diagnosis of hemochromatosis. But the serum iron was normal and the biopsy results were normal Dr Epps regards these as being against the diagnosis. My own personal view would be that they completely exclude it I put this as an argument against Dr Epps main diagnosis.

Then I wonder whether Dr Epps could explain the friction rub which was heard at the time of the patient's admission to the hospital. I fear that that is hard to fit into the diagnosis of hemochromatosis

DR. EPPS Well I presumed perhaps wrongly that this was in fact a murmur and not a pericardial friction rub. It is stated that a little later a mitral murmur was present There is possibly some doubt about it. I prefer to leave it open

DR. STUCKEY Just one or two brief comments firstly on possible tests which might help to elucidate the diagnosis in this sort of situation

Removal of pericardial fluid for diagnostic purposes is entirely justifiable. If one believes that there is any free fluid in the pericardial sac at all even if it is not a problem therapeutically one is justified I think to remove some for examination Blood-stained fluid suggests the possibility of malignant disease and occasionally tumor cells can be found in fluid withdrawn from the pericardial sac I have seen a diagnosis of malignant disease in the myocardium made in this way on at least two occasions

Another diagnostic measure that should come up for consideration I think is



Fig. 3. Section through right coronary artery showing almost complete obstruction by atheroma and a little organizing blood clot. Stained with hematoxylin and eosin. X30

myocardial biopsy. This has not really caught on yet, but I think that it is justified and could be considered in this sort of situation in which the disease is fairly obviously myocardial and almost certainly diffuse and in which all other reasonable tests have been made and no positive conclusion has been reached. It can be done rather simply—it is a fairly minor surgical procedure. A small portion of myocardium taken at biopsy for microscopic examination would almost certainly give the final answer.

DR. AMOS. We have heard that this man had a diabetic type of glucose tolerance. I am wondering whether he had any glycosuria and whether insulin treatment was required. This is not mentioned in the protocol. I wonder whether Dr. Isbister or Dr. Rowe could tell us about this.

MODERATOR. Could we hear at the same time please whether the patient was febrile at any stage of his illness?

DR. ROWE. This patient was slightly febrile for about 18 hours after admission to the hospital, after which he lost his fever. He did have glycosuria on odd occasions throughout his stay in the hospital but only to the extent of 1/4 to 1/2 per cent. This required no treatment.

MODERATOR. Let us hear Dr. Evans.

DR. EVANS. I won't detain you long. I will tell you first about the heart, which I think you would wish me to do, and apart from that there is little to tell.

The heart was moderately enlarged, as Dr. Epps has indicated. It weighed sixteen ounces (450 grams), the average normal being 10½ ounces (300 grams). The main finding was that the lumen of the right coronary artery and the lumen of the anterior descending branch of the left coronary artery were both almost completely blocked by atheroma (Fig. 3). The anterior wall of the left ventricle near the apex was extremely thin, measuring only 2 mm. (Fig. 4). There was discoloration of the septum—it is a little difficult to see now—a sort of reddish mottling that was noticeable immediately when the heart was opened, and a few little white streaks could be seen running through it.

Microscopy of sections taken from the thin part of the left ventricle showed old fibrosis, with contraction and very few



Fig. 4. The heart, laid open to show the extreme thinness of the left ventricular wall near the apex.



Fig. 5. Section through the wall of the left ventricle near the apex showing extensive fibrosis. Van Gieson stain. ×30.

MODERATOR: What was the condition of the uninfarcted part of the heart muscle?

DR. EVANS: The remainder of the heart muscle was not examined microscopically.

DR. ROWE: The curious thing is that this patient had no pain in the chest in the few days before his death. The severe pain that he had had some 4½ months prior to his admission to the hospital was described as starting near the medial border of the left scapula and radiating round under the axilla to the front of the chest. There was also a little bit of radiation into the medial aspect of the left arm. We could not satisfactorily interpret this. His pain during the second illness 2 months later was described as being much the same, but it soon subsided. After that he had no more chest pain until he died.

Clinical diagnosis: Congestive heart failure probably due to rheumatic carditis.

Dr Epps' diagnosis: Hemochromatosis affecting the heart.

Other suggested diagnoses: Tumor of the

urviving muscle fibers (Fig. 5). A section taken from the interventricular septum showed the presence of old fibrous and also scattered areas of recent necrosis of muscle fibers surrounded by polymorphonuclear infiltration, indicating that the infarct was some days old—say, 24 hours to a few days old (Fig. 6).

Lastly, as far as the heart is concerned, there was a little antemortem clot in the right atrium (atrial appendage); this was quite firmly fixed and had been there for some time.

The alveoli of the lungs showed some mild congestion, with perhaps a slight increase in fibrous tissue in their walls. There were a few heart failure cells in the alveoli. The lungs were otherwise normal. The abdominal viscera were all a little congested, but there was nothing special to record on macroscopic or microscopic examination.

The postmortem diagnosis then was coronary arterial occlusion with myocardial infarction superimposed on old fibrosis.



Fig. 6. Section through the interventricular septum showing muscle necrosis and polymorphonuclear infiltration. Stained with hematoxylin and eosin. ×130.

heart (Dr Kraus and Dr Vincent) conduction defect leading to fatal disorder of rhythm (Dr Vincent) drug-induced hypokalemia leading to fatal disorder of rhythm (Dr Anderson)

Anatomic diagnosis Atheromatous occlusion of coronary arteries leading to fibrosis of the left ventricle and septum of the heart together with areas of recent necrosis of the septum.

Problems in the diagnosis of cor pulmonale

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Chronic respiratory diseases, in particular chronic bronchitis and pulmonary emphysema, are becoming increasingly more frequent problems for the physician. Causative factors in this trend appear to be the advancing age of the population and continued exposure to respiratory irritants, including heavy cigarette smoking. As pulmonary disease advances in an individual, the heart is eventually subjected to the stresses of the altered physiology. At this stage the presence of respiratory disease is usually not difficult to diagnose, but it may be exceedingly difficult to recognize at an early stage the time at which the heart becomes pathologically involved. This is one form of "cor pulmonale," but just what other types of heart disease should be included in this designation has been the subject of considerable debate. Indeed, there is no universal agreement on the definition of cor pulmonale.

One common definition of cor pulmonale is: The pathologic (as opposed to physiologic) right ventricular changes (hypertrophy, dilatation, failure) due to disorders of the lungs, of the pulmonary vasculature, or of the chest wall. Another definition suggested by the World Health Organization is "Hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease." Perhaps abnormal right ventricular dilatation (with or without hypertrophy) should also be included in this definition. It should be noted that, as defined, such diseases as mitral stenosis would be excluded as causes of cor pulmonale.

The discussions to follow will be restricted largely to *chronic* cor pulmonale as opposed to the subacute (e.g., carcinomatous infiltration of the pulmonary vasculature) or the acute (e.g., acute pulmonary embolism) varieties of the disease. More specifically, the restriction will be to *chronic cor pulmonale* due to *diffuse obstructive pulmonary emphysema.* This is certainly the most important from the standpoint of incidence and the most unique from the standpoint of diagnostic difficulties. In delineating these restrictions, *no attempt* is made to settle the semantic confusion over the use of the terms "emphysema" and "chronic bronchitis" as they are applied to clinical or pathologic material. This problem is being actively debated, and interesting new data to help in its resolution are being accumulated. Perhaps surprising to some are the findings of a recent study in which patients with "chronic bronchitis" but without evidence of emphysema had more severe blood-gas changes and more prominent right heart

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failure than did a group of patients with primary emphysema without chronic bronchitis.[3]

Regardless of the confusion that presently exists, it seems clear that the great majority of patients in whom diffuse obstructive emphysema is diagnosed clinically has also a significant amount of chronic bronchitis with or without bronchiectasis. Thus, in the discussions to follow the term emphysema is used to imply chronic pulmonary disease in which both emphysema and chronic bronchitis are usually present to a significant degree.

Pathophysiology

The pathophysiology of cor pulmonale due to pulmonary emphysema is exceedingly complex, and no attempt will be made here to discuss in detail the many factors involved. An oversimplified schema is summarized in Fig 1 The two basic etiological factors at work to produce right ventricular abnormalities are (1) right ventricular pressure work, and (2) right ventricular volume work. Of the two by far the more important is right ventricular pressure work, but, as will be seen from the standpoint of electrocardiography the concept of right ventricular volume work is significant.

Right ventricular pressure work (increased pulmonary arterial pressure) is related to (1) decreased size of the pulmonary vascular bed and (2) *relatively* increased pulmonary blood flow Decreased size of the pulmonary vascular bed may be due to structural factors (anatomic alteration of areas of the pulmonary vasculature) or to functional factors (pulmonary arteriolar constriction) Relative increase in pulmonary blood flow may be caused by anoxia, hypercapnia, fever infection emotional factors labored breathing increased blood volume, use of sympathomimetic bronchodilators etc. Right ventricular pressure work (pulmonary arterial hypertension) is basically determined by an increased pulmonary vascular resistance in relation to pulmonary blood flow In creased vascular resistance is *determined* by such factors as (1) bronchial obstruction with alveolar distention leading to capillary narrowing (2) arteriolar constriction, probably caused at least in part by anoxia and hypercapnia (3) increased blood viscosity (polycythemia) (4) parenchymal destruction and structural vascular alterations, (5) intrapulmonary vascular shunts and (6) decreased vascular distensibility

Right ventricular volume work is related to such factors as increased blood volume increased cardiac output and the presence of ventricular dilatation

An accurate complete presentation of the relationship and interrelationships of the above-mentioned and other important factors in the development of cor pulmonale is almost impossible. Because of the complexities of the pathophysiology of cor pulmonale and for the purpose of this discussion it would seem more appropriate to think in terms of the two basic causative factors as noted above right ventricular pressure work and right *ventricular volume* work of which the former is by far the more important It is obvious of course that the normal right ventricle is constantly doing pressure work and volume work (as are all the chambers of *the heart)* but this is work which is *normal and in*volves an amount of work *to which the* right ventricle is well adapted At some point under the *influence of* disease the work loads become excessive, and the response of the right ventricle is manifested anatomically by hypertrophy For a time *these excessive loads* may exist only under *stress* (e.g exercise) but with advancing disease they are present even at rest. The important concept then is that in the presence of these causative factors of disease and after a period of time right ven*tricular* abnormalities begin to appear (Fig 1) This is cor pulmonale. Attempts *should* be made to diagnose it at the earliest possible stage. Later through a *series of* complex, incompletely understood mechanisms the right ventricle fails. Diagnosis at this stage is not difficult

In considering the pathophysiology of cor pulmonale one might make an analogy *to the* systemic circulation There would be systemic arterial hypertension without demonstrable left ventricular abnormalities. This might be termed simply systemic arterial hypertension Later left ventricular abnormalities (dilatation hypertrophy) appear. This

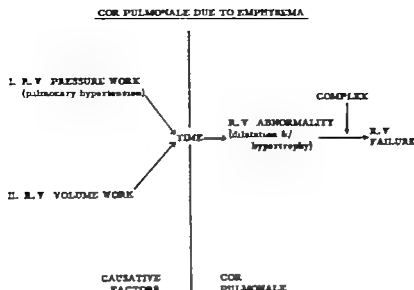


Fig. 1. Simple schematic representation of the basic factors responsible for the development of cor pulmonale. Consult text for details.

hypertensive cardiovascular disease." Carrying the analogy to the right side of the heart and pulmonary circulation there would be pulmonary arterial hypertension and later cor pulmonale.

Diagnosis of cor pulmonale due to pulmonary emphysema

The necessity for early diagnosis of cor pulmonale is obvious. Its presence implies a severe degree of pulmonary disease and dictates the need for early, proper, and intensive cardiac and pulmonary therapy. Prognostic implications are obvious.

From the diagnostic standpoint, two important questions emerge: (1) In the presence of the causative factors (Fig. 1) when does the right ventricle first become pathologically involved? (2) When and how do the clinical cardiac findings of cor pulmonale develop distinct from the pulmonary findings of emphysema alone?

As will be seen, when cor pulmonale is due to emphysema, an early diagnosis is usually more difficult to make than when it is due to other causes, such as pulmonary emboli, primary pulmonary hypertension, or diffuse pulmonary fibrosis. This is because *the presence of emphysema tends to obscure the diagnostic features of cor pulmonale.* This is the central theme of the following discussion. This is really the unique problem, since the presence of emphysema effectively tends to mask the historical findings, the physical findings, and the laboratory manifestations of cor pulmonale, including radiologic and electrocardiographic features. The problems encountered in employing each of these diagnostic means will be analyzed separately.

The diagnosis of cor pulmonale must often be based not only on direct but also on indirect evidence, as will be seen. This includes features associated with cor pulmonale frequently enough to be of predictive value, but not necessarily diagnostic or pathognomonic of its presence.

Symptoms. By the time cor pulmonale is present, one would expect the *symptoms of emphysema and chronic bronchitis* to be evident, such as chronic cough, increased sputum, recurrent infections, etc.

Dyspnea is difficult to evaluate. This could obviously be present with emphysema alone, whether or not heart disease is present. Occasionally, however, because of mechanisms which are not evident, the development of right ventricular failure is manifested by increasing dyspnea, decreasing exercise tolerance, and especially increasing orthopnea.

Pain is an important symptom. *Epigastric pain* and some substernal discomfort are not uncommon in emphysema without cor pulmonale. The causes of the pain are

not clear but many appear to be musculoskeletal in nature possibly related to the increased work of breathing and trauma from coughing. It is also worth remembering that gastrointestinal peptic ulceration is relatively frequent in emphysema. As opposed to epigastric discomfort, however, when *right upper quadrant pain* develops it may signify that hepatic congestion is present. This would indicate the presence of right ventricular failure. Significant *substernal pain* in emphysema can probably be caused directly or indirectly by right ventricular ischemia and by pulmonary hypertension. Pulmonary hypertension as an etiological factor must be relatively less important since pulmonary arterial pressure in emphysema usually does not reach very high levels in contrast to some other causes of cor pulmonale. Nevertheless, if it should occur it would imply marked pulmonary hypertension and by this time cor pulmonale would certainly be present.

The sensation of *fatigue* is often masked by the presence of dyspnea. Furthermore fatigue may be present in emphysema without cor pulmonale. Nevertheless, a marked increase in the degree of fatigability frequently denotes the onset of right ventricular failure.

In emphysema, *disorientation and changes in the level of consciousness* imply severe changes in the blood gases. Cor pulmonale is usually present at this stage.

Physical findings. By the time cor pulmonale is present, the physical findings of *emphysema* are usually quite evident. These are well known and will not be discussed.

Observations of the *venous system* are important. Because of the altered ventilatory mechanics in patients with emphysema rather marked distention of the neck veins may be present in the absence of cor pulmonale or right ventricular failure. This may lead to confusion. It will be noted however that the venous distention is present only during expiration (and at the very end of inspiration in some patients) and there is a very marked collapse of the neck veins on inspiration. Thus, typically in emphysema there are exaggerated excursions of the neck veins during respiration. When marked right ventricular failure occurs however the excursions are diminished and the veins tend to remain distended during the entire respiratory cycle and also when respiration is suspended temporarily in mid inspiration in a relaxed manner. Finding that the distended neck veins fill from below during these maneuvers can be helpful. In addition the hepatojugular reflux with a subject relaxed revealing increasing distention of the neck veins after pressure over the liver may be helpful in indicating a distended right venous system and thus right ventricular failure. In all interpretations of the venous system one must remember the relationships to body position (lying sitting erect sitting semierect etc.) and to the phlebostatic axis.

Detection of *edema* may be *helpful or* misleading. Ankle edema may be present in emphysema without right ventricular failure especially in *older people if the* patient tends to sit immobile for long periods. Rapidly increasing and or severe edema in emphysema however is usually a reliable sign of right ventricular congestive failure. Likewise a careful serial record of a patient's weight may be helpful in that an unexplained gain in weight may be caused by the accumulation of fluid due to right ventricular failure.

The presence of *cyanosis* may be helpful by association. By the time this is evident cor pulmonale is usually present. Cyanosis in emphysema implies severe alterations in blood gases and usually is associated with some polycythemia. Cyanosis is more striking in cor pulmonale due to emphysema than in right ventricular failure due to other causes.

Observations concerning the *liver* may be helpful but again the obscuring *effects of* emphysema must be recalled. In emphysema when the edge of the liver is palpable below the costal margin the problem is whether the liver is of normal size and simply displaced downward by a depressed diaphragm or whether the *liver* is enlarged and congested from right ventricular failure of cor pulmonale. Measurements may be helpful. In the mid-clavicular line the distance from the change in percussion note over the top of the liver to the lower edge of the liver (during the same phase of respiration) should *normally* measure

less than 10 to 12 cm. (depending on body size and build). If congested, the liver frequently measures more than this. Furthermore, especially if congestion has been rather acute, the liver may be quite tender. In addition, the character of the palpable edge may be helpful in that when the liver is congested, the edge may be somewhat blunted. Sometimes the detection of congestive *splenomegaly* can also help to decide whether a palpable liver is also congested.

For the degree of peripheral edema frequently encountered in emphysema with cor pulmonale and failure, *hydrothorax* is unusual. When in this situation effusion is present as a transudate, it means cardiac failure and usually failure of both ventricles.

Interpretation of *precordial and epigastric percussion and palpation* may be difficult in the presence of emphysema. Again, because of the presence of intervening overinflated lungs and associated thoracic deformity, emphysema tends to obscure the signs of right ventricular abnormalities. Also, this is again in contrast to right ventricular abnormalities due to other causes, in which instances, for example, a hypertrophied right ventricle is frequently readily evident by precordial palpation. Patients with emphysema and a low diaphragm, however, often have a pronounced systolic footward forward thrust of the inferior cardiac border which correlates well with the presence of cor pulmonale. This is readily felt in the epigastrium but must be distinguished from the forward pulsation of the abdominal aorta. When one places the hand flat in the epigastrium and presses inward and upward, a pulse on the tip of the fingers from the right ventricle can usually be differentiated from a pulse on the palmar surface produced by the abdominal aorta. By the time that tricuspid insufficiency develops during the course of pulmonary hypertension, the diagnosis of cor pulmonale is usually quite evident. In such patients, one should note the right subcostal systolic movement of the liver due to the tricuspid insufficiency. This should be differentiated from a directly transmitted cardiac impulse. This is done partly by comparing the time of the liver pulse with that of the carotid pulse. In tricuspid insufficiency, pulsation of the liver is detected slightly later than the carotid pulse.

At certain stages in the development of cor pulmonale due to emphysema (particularly if the right ventricle has not yet failed), one may be able to detect *signs of increased cardiac output* (hyperkinetic state). These include wide pulse pressure, increased peripheral arterial pulsations (more appreciable in the digital arteries), sharp loud heart sounds in the epigastrium, hyperactive cardiac epigastric pulsations, and warm dry palms (in contrast to the findings in other common forms of heart failure). To what degree these findings in certain patients are due directly to cor pulmonale itself or are due to associated features, such as infection, fever, the use of sympathomimetic drugs, and the like, remains to be clarified.

Auscultation of the heart is exceedingly important but may be hampered by the presence of emphysema. Again, as in other aspects of the examination, the presence of emphysema, with the hyperinflated intervening lung, tends to obscure important auscultatory phenomena which originate in the heart. For obvious reasons, these manifestations are usually displaced to the epigastrium and may be detectable only in that area.

Heart sounds are usually distant, but with pulmonary hypertension an accentuated pulmonic second sound (relative to the aortic second sound) may be noted, usually in the epigastrium.

Gallop sounds are frequent in emphysema and originate from the right side of the heart.[3] Their presence implies the existence of at least early cor pulmonale, although they may be present without other signs of right ventricular failure. Thus they are of much diagnostic importance. The gallops from the right side of the heart are of two basic types: (1) the atrial or fourth heart sound gallop which occurs in presystole and (2) the ventricular or third heart sound gallop which occurs in early diastole.[4] These sounds are similar to gallops from the left side except that their origin from the right side of the heart is diagnosed by their location in the epigastrium and their tendency to increase in intensity on inspiration and decrease on expiration. Gal

lops from the left side of the heart show the reverse respiratory variation.[6]

Pulmonary systolic clicks ("systolic gallops") are frequent with pulmonary hypertension but again in emphysema their detection is hampered by the hyperinflated lung. They may be heard occasionally in the epigastrium and as opposed to diastolic gallops on the right side they tend to increase in intensity on expiration.

Important *murmurs* e.g., those due to aortic stenosis, may be missed because of emphysema. The detection of the murmur of tricuspid insufficiency in the presence of emphysema is important. It implies severe cor pulmonale with right ventricular dilatation. This murmur is usually loudest in the epigastrium and tends to increase in intensity on inspiration and decrease on expiration. The murmur of mitral insufficiency shows the reverse respiratory variations and this helps in its differentiation from the murmur of tricuspid insufficiency.

Clinical laboratory studies

Blood studies. Important blood studies in the evaluation of patients with emphysema include determinations of hematocrit and hemoglobin and studies of CO_2 combining power and chlorides and arterial O_2 saturation, pCO_2, and pH determinations. Blood studies are important in the diagnosis of cor pulmonale due to emphysema because of association. Generally by the time significant polycythemia and sustained arterial O_2 unsaturation and hypercapnia are present (especially at rest) significant cor pulmonale is usually present.[7]

Venous pressure. It is necessary to realize the influence of respiration on venous pressure in emphysema. Because of marked respiratory variations in venous pressure which may amount to 40 mm. H_2O or more venous pressure should be measured at least during relaxed suspended respiration. Furthermore, in emphysema, because of the increased anteroposterior diameter of the chest the reference level (phlebostatic axis) is frequently misjudged and the level of venous pressure is usually underestimated. When measured carefully however this determination may help one to suspect the presence of cor pulmonale with right ventricular failure.

Circulation time. This determination is not of great value in the diagnosis of cor pulmonale. If significant cor pulmonale with right ventricular failure is present however the arm-to-tongue circulation time (e.g., with Decholin) is likely to be prolonged, but cor pulmonale affects primarily the arm-to-lung time (ether-saline) whereas the lung-to-tongue time is near normal. This is in contrast to left ventricular failure.

Radiologic findings. By the time cor pulmonale is present, the radiologic findings of emphysema are usually evident. These are well known and will not be discussed.

The detection of abnormalities in the *pulmonary vasculature* implies the presence of significant pulmonary hypertension but does not necessarily mean that cor pulmonale is present although it frequently is. Pulmonary vascular abnormalities consist chiefly of an increase in the size of the main pulmonary artery and its major branches, with some decrease in the size and detectable presence of the peripheral pulmonary vessels.

Early radiologic detection of *cardiac abnormalities* may be exceedingly difficult in the presence of emphysema. Because the heart is pulled downward by the low diaphragms and the chest volume is increased cardiac enlargement *may* be difficult to estimate. Furthermore, since the right ventricle is located anteriorly the erect posteroanterior view is not well suited for detection of abnormalities of this chamber. Even in the lateral view the increased anteroposterior diameter of the chest in emphysema may cause the size of the right ventricle to be misjudged. It should be stressed that in emphysema, the size of the heart may appear to be perfectly normal by chest x-ray examination in spite of rather marked right ventricular hypertrophy. Of obvious importance in the radiologic diagnosis of cor pulmonale are serial radiographic studies. The typical x-ray findings of cor pulmonale would be widening of the heart shadow with slight upward tilt of the apex (or a "squaring off" of the left border) on the posteroanterior view, a forward bulge of the right ventricle in the oblique and lateral views and the presence of the "right ventricular shelf" in the left anterior oblique view

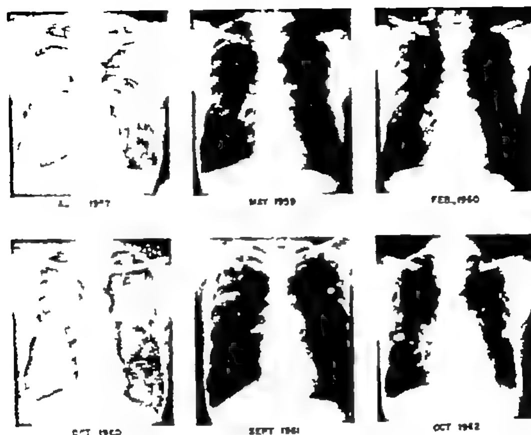


Fig. 2. Serial teleroentgenograms in patient with progressive emphysema and cor pulmonale. Consult text for details.

The importance of serial films is well demonstrated in Fig. — (This figure should be compared with serial electrocardiograms taken on this same patient Fig. 4.) In August 195 the findings of emphysema and pulmonary hypertension (with large pulmonary artery and main branches) are evident but it would be difficult to be certain that the heart was enlarged. It should be recalled that a low diaphragm and a ptotic heart tend to accentuate the prominence of the pulmonary conus and main pulmonary artery in the normal individual. In May 1959 there was a slight change in the size of the heart but on the basis of this film alone it would be difficult to say that cardiomegaly was present. The electrocardiogram at this time showed evidence of emphysema but did not show definite right ventricular hypertrophy. By February 1960 in association with a pulmonary infection the heart was slightly enlarged radiologically. The electrocardiogram at that time was suggestive of right hypertrophy but not definitely so. In October 1960 the size of the heart is decreased and is similar to what it was in August 195. This shows that the right ventricle is capable of significant reversible dilatation. Interestingly enough the electrocardiogram at that time showed very convincing evidence of cor pulmonale (right ventricular hypertrophy). From October 1960 through September 1961 and October 196-, both the chest x-ray films and the electrocardiograms showed progressive right ventricular enlargement. By October 1962 there was no difficulty in diagnosing cardiomegaly by x-ray examination although right ventricular abnormalities had been present for years.

Electrocardiography. In the interpretation of the electrocardiogram in the presence of emphysema several points are worth great stress. First an important problem is to

realize that ***emphysema itself produces alterations in the electrocardiogram even though cor pulmonale is absent.*** Thus, the criteria for the diagnosis of right ventricular hypertrophy must be separated from those of emphysema alone. Secondly, it is important to recall that since emphysema alone does alter the electrocardiogram, it tends to obscure the electrocardiographic manifestations of right ventricular hypertrophy. This is in contrast to right ventricular hypertrophy due to other causes. Therefore, somewhat different criteria are needed for the diagnosis of right ventricular abnormalities when these are caused by emphysema. Thirdly, it should be noted that the electrocardiogram may appear to be perfectly normal even in the presence of significant cor pulmonale. Lastly, and at the other end of the spectrum, it is important to realize that emphysema and cor pulmonale may alter the electrocardiogram to such a degree that grossly erroneous interpretations may be made, as, for instance, that of myocardial infarction when this is not actually present.[3]

The concepts of ventricular pressure work (systolic overload) and ventricular volume work (diastolic overload) and their relationships to the electrocardiogram have recently received much emphasis. With reference to the right side of the circulation, atrial septal defect offers the classic example of right ventricle diastolic overload, and pulmonary stenosis or primary pulmonary hypertension the classic examples of right ventricular systolic overload. The function of the crista supraventricularis is important

EMPHYSEMA AND HYPERTROPHY OF THE CRISTA SUPRAVENTRICULARIS

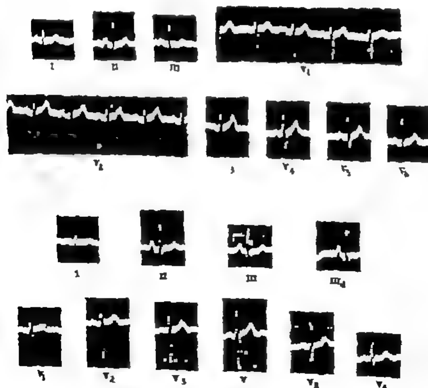


Fig. 3. Two sets of electrocardiograms from the same patient with emphysema recorded about 4 years apart (*top*, 1957; *bottom*, 1961). These tracings illustrate the electrocardiographic manifestations of pulmonary emphysema. In addition, careful study of the lower tracing reveals evidence for hypertrophy of the crista supraventricularis. Consult text for details.

in an understanding of these differences. The crista supraventricularis is a band of muscle in the right ventricle which has its base under the pulmonary valve in the outflow tract and which has two arms one running down the septum and the other down the right ventricular free wall The crista seems to be concerned primarily with volume work. Thus in atrial septal defect with considerable volume overloading of the right ventricle (when the right ventricle may carry several times more blood than the left) but without pulmonary hypertension the right ventricular free wall may appear to be almost entirely normal. In such cases, however the crista supraventricularis reflects volume overload by its hypertrophy [9] Electrocardiographically this is expressed by a late vector to the right and anterior and it is seen as the classic R (RSR′) pattern in V_1 of atrial septal defect.

In pressure overloading of the right ventricle such as occurs in pulmonary stenosis or primary pulmonary hypertension the entire right ventricle seems to participate including both the free wall and the crista supraventricularis. This is manifested electrocardiographically as the classic pattern of right ventricular hypertrophy with an R/S ratio in the right precordial leads greater than unity and with a dominant R wave pattern (Rs R qR QR qRs)

In the right ventricular hypertrophy (cor pulmonale) of pulmonary emphysema as pointed out earlier two basic causative factors are at work. One is a pressure load and the other is a volume load The more important of the two is the pressure load but it is not infrequent at autopsy to discover a right ventricle which seems to have reflected primarily a volume load namely with hypertrophy of the crista supraventricularis and a normal or nearly normal right ventricular free wall. Evidence is available that this response may be detected electrocardiographically This shall be discussed in more detail later At present suffice it to say that hypertrophy of the crista supraventricularis should be considered as an abnormality of the right ventricle, and thus in emphysema is evidence of cor pulmonale Perhaps in these instances it is reflecting a hypervolemic or high-output (hyperkinetic) state or both In passing it might be mentioned that there is much evidence both supporting and refuting the presence of an increased cardiac output in cor pulmonale of emphysema The many factors affecting cardiac output are probably to blame for these discrepancies and individual variations may be great. Factors other than emphysema itself which may be important are fever infection emotional reactions, anoxia hypercapnia hypervolemia labored breathing the use of sympathomimetic drugs etc.

With these considerations in mind the major part of the evidence tends to support the concept that there is at least a relative increase in cardiac output in these states for the degree of failure regardless of what the cause of this increased output may be. The problem is unsettled however

Another concept that might be remembered is that the right ventricle is primarily suited for volume work and the left ventricle for pressure work.[11] Relatively speaking the left ventricle becomes abnormal more readily under a volume load than does the right, and the right ventricle becomes abnormal more readily under a pressure load than does the left.[11] Nevertheless as pointed out the right ventricle may express its volume load through hypertrophy of the crista supraventricularis at an early stage

From what has been stated above it will be clear that the electrocardiographic manifestations of right ventricular abnormality (hypertrophy of the free wall and/or hypertrophy of the crista supraventricularis) will depend somewhat upon the underlying etiology and associated disease (e.g atrial septal defect vs. pulmonary stenosis vs. cor pulmonale due to primary pulmonary hypertension vs. cor pulmonale due to emphysema)

It has been pointed out[12] that in emphysema the heart becomes vertically placed because of the low diaphragm. This results in a vertical electrical position of the heart and a rightward deviation of the mean QRS and P wave axis in the frontal plane Because of the low lying position of the heart the usual precordial lead positions will be high resulting in part in these leads lying in an area of relative negativity for the mean QRS vector Thus pre

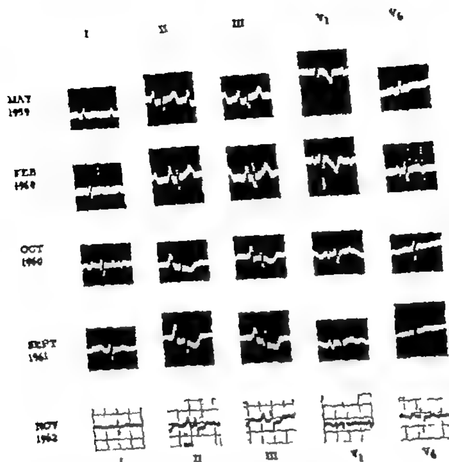


Fig 4 Serial electrocardiograms recorded from patient with emphysema and progressive cor pulmonale. This should be studied in association with Fig 2, hich how serial teleroentgenograms of the same patient. Consult text for details.

dominantly negative QRS deflections will be recorded in Leads V_1-V_6. It has also been pointed out that posterior rotation of the mean QRS vector in the horizontal plane also contributes to a shift in the transition zone to the left in emphysema (marked clockwise rotation).[22] With a shifting of the heart to the vertical position there is a tendency for electrical clockwise rotation on the longitudinal axis and the appearance of the S_1Q_3 pattern. Finally in emphysema the QRS voltage is low because the electrodes are relatively far removed from the ventricles since the emphysematous lung is a poor electrical conductor and since the QRS-E loop tends to be posteriorly oriented with a resultant small projection on the frontal plane.[11] In general, the effects of emphysema on the electrocardiogram appear to be due to two basic factors a change in the anatomic position of the heart (vertical displacement associated with a low diaphragm) and the intervention of a hyperinflated lung.

It is readily apparent therefore that emphysema may alter markedly the electrocardiogram in the absence of cor pulmonale furthermore and just as important, it tends to obscure the usually accepted electrocardiographic manifestations of right ventricular hypertrophy.

The electrocardiographic criteria for the diagnosis of emphysema must be separated from the criteria for the diagnosis of right ventricular hypertrophy in the presence of emphysema. From the studies of others[23-26] and from our own experience the following would appear to be acceptable with our present state of knowledge.

ELECTROCARDIOGRAPHIC MANIFESTATIONS OF EMPHYSEMA (1) Increased amplitude and/or tented P waves in Leads II III

GIANT P WAVES WITHOUT RIGHT VENTRICULAR HYPERTROPHY

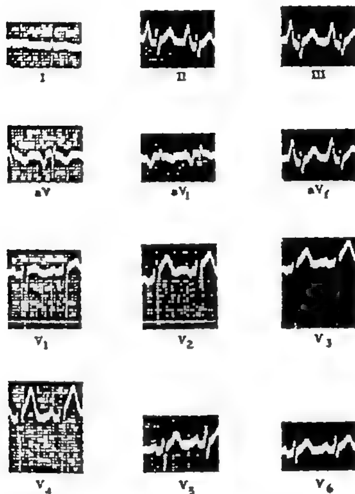


Fig. 5. Giant P waves occurring in a patient with emphysema. Subsequent autopsy revealed a normal right ventricle. Consult text for details.

and aV$_F$. Flat P in Lead I. Inverted P in Lead aV$_L$. P axis +60 to +90 degrees in the frontal plane but especially greater than +80 degrees. (2) Increased amplitude of the T waves in Leads II, III, and aV$_F$. (3) Tendency to right axis deviation of the mean electrical axis of the QRS complex. (4) Clockwise rotation in the precordial leads (leftward shift of the transition zone). (5) Low voltage of the QRS, especially in Lead I and the left precordial leads ("fall off" in voltage laterally). (6) Increasing amplitude and/or increased tenting of the P wave in Lead IIId (Lead III recorded with deep held inspiration) as compared with Lead III. (7) Marked respiratory variation of QRS amplitude, usually in Leads V$_1$ and V$_2$. (8) Failure to lose or change a great deal a Q wave from Lead III to Lead IIId. Little respiratory variation of QRS complexes in Lead III.

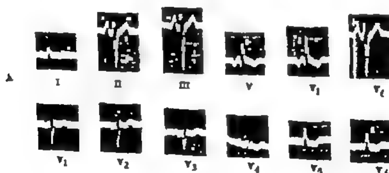
The electrocardiographic manifestations of emphysema in a mild to moderate form are well illustrated in Fig. 3. These two sets of electrocardiograms from the same patient with emphysema were recorded about 4 years apart (top tracings in 1957, bottom tracings in 1961). The lower tracings show increased amplitude of the P wave in Leads II and III with some increase in the T wave in Lead II and a flat P in Lead I. There is a tendency to right axis deviation

the transition zone is shifted slightly to the left in the V leads, and there is low QRS voltage in Lead I and a fall-off in voltage laterally to Lead V_6. In Lead IIId the P wave becomes more pointed and there is little change in the Q wave (or the whole QRS for that matter) when compared with Lead III. The top tracing shows respiratory variation of QRS amplitude in Leads V_1–V_5.

These changes are typical of emphysema. The mechanisms for some of these are described above. The exact reasons for the increased respiratory variation in the QRS complexes in the V leads and for increased tenting of the P waves in Lead IIId are not completely clear. Failure of the Q wave to change from Lead III to Lead IIId is probably related to a rather low fixed diaphragm. In fact, it is very unusual to detect much respiratory variation of the QRS complexes in Lead III when significant emphysema is present.

The above-described changes may occur in the electrocardiogram of a patient with emphysema but without necessarily any right ventricular hypertrophy (cor pulmonale). It is clear that another set of criteria must be employed to recognize the presence of right ventricular hypertrophy in such situations. Again, from the experience of others[?] and our own, the following criteria would seem to have merit. Some offer direct evidence for the existence of right hypertrophy, whereas others present only indirect evidence for its presence. Some probably reflect right ventricular hypertrophy directly, whereas others relate possibly to right ventricular dilatation or to rotatory events frequently associated with cor pulmonale.

AXIS ILLUSION PHENOMENON IN EMPHYSEMA



ANTEROSEPTAL MYOCARDIAL INFARCTION

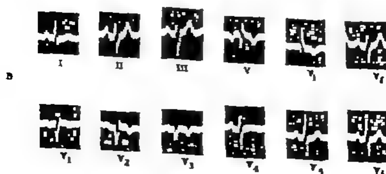


Fig. 6. *A*. Axis illusion phenomenon occurring in patient with emphysema and cor pulmonale. Note the apparent marked left axis deviation and possible anteroseptal infarct. Consult text for details. *B*. True anteroseptal myocardial infarction. Compare with *A*.

ELECTROCARDIOGRAPHIC CRITERIA FOR THE DIAGNOSIS OF COR PULMONALE DUE TO EMPHYSEMA

Fairly conclusive (1) Classic right ventricular hypertrophy with R/S ratio in right precordial leads (V₁ V₂ V₃) greater than unity (in some patients the earliest change may be in V₃R) Dominant R wave pattern (Rs R qR QR, qRs) in these leads. (2) Incomplete right bundle branch block with rSR in right precordial leads with QRS duration less than 0.12 second (3) Tendency to right axis deviation of the QRS in a heart radiologically enlarged

Strongly suggestive (1) Marked right axis deviation (greater than +110 degrees) (2) Axis illusion phenomenon (3) Crista supraventricularis hypertrophy (wide S in Leads I II III V₅ and V₆) (4) QS Qr or qr patterns in Leads V₁ V₂ (in absence of anteroseptal infarction) (5) R/S ratio in Lead V₆ less than unity

Suggestive (1) Giant P pulmonale. (2) Right bundle branch block (QRS duration greater than 0.12 second) especially if R in Lead V₁ exceeds 10 mm. in amplitude (3) Right ventricular conduction disturbances (e.g. right bundle branch block patterns) with atrial or nodal premature contractions. (4) Well-developed R' or embryonic R' in right precordial leads. (5) Marked shortening of S in Lead V₁ (6) Infarct Q waves (0.04 second or more in duration) in Leads II III and aV$_F$ (in the absence of posterior infarct) (7) Deep S in Lead I and deep Q in Lead III (8) q/R ratio less than unity or R/S ratio greater than unity in Lead aV$_R$

The origins of some of the criteria listed above are obvious and need no further comment Others for example in the suggestive categories have not been subjected to rigorous statistical analysis and thus must remain in the realm of "impressions." It should be noted that the combination of several "suggestive" criteria may amplify the diagnostic accuracy

A few illustrations are in order Fig 4 depicts serial electrocardiographic evidence of the development of right ventricular hypertrophy in a patient with emphysema In May 1959 electrocardiographic findings typical of emphysema are present but there is no conclusive evidence of cor pulmonale The P waves and T waves are prominent in Leads II and III and the P wave is flat in Lead I There is low QRS voltage in Leads I and V₆. By February 1960 there is right axis deviation and the R/S ratio in Lead V₆ is less than unity By October 1960 there is more right axis deviation the R/S ratio in Lead V₆ is less and there is an embryonic R' wave in Lead V₁ The changes are now fairly suggestive of cor pulmonale (at this time as shown in Fig 2 the heart size on the x-ray film was completely normal) By September 1961 a qrs pattern is present in Lead V₁ and by November 1962 the classic pattern of right ventricular hypertrophy is present in this lead with a qR pattern and an R/S ratio greater than unity At this time for all practical purposes, cor pulmonale is definite.

Fig 5 demonstrates the unreliability of inferring right ventricular hypertrophy in the electrocardiogram from changes potentially due to emphysema. Among other features, the giant P waves are striking in this tracing However although this patient had significant emphysema at autopsy the heart weighed only *273* grams, and the right ventricle was normal. Thus, P wave amplitude may be unreliable in indicating the presence of right ventricular hypertrophy In fact in several tracings from patients with cor pulmonale decreasing amplitude of the P wave is frequently observed as evidence of right ventricular hypertrophy progresses.

Fig 6,*A* illustrates the so-called axis illusion phenomena the mechanism of which is not clear but has been debated.[12,14] Simply it is recognized in a tracing which demonstrates many of the features of emphysema but also the presence of a rather marked left axis deviation when right axis deviation might have been anticipated In this record the P waves and T waves are prominent in Leads II III and aV$_F$ the P wave is flat in Lead I and inverted in Lead aV$_L$, the QRS voltage is relatively low in Leads I and V₆ and the transition zone is displaced to the left in the V leads. These findings are compatible with pulmonary emphysema yet there is apparent marked left axis deviation It has been our experience that the large majority of patients with emphysema with these electro-

cardiographic findings has significant cor pulmonale. Another interesting finding is evident in the tracings. Leads V_1 through V show large QS waves raising the possibility of an anteroseptal myocardial infarction. This type of pattern is not infrequent, however, in the axis illusion phenomenon in the absence of infarction and may be taken as further evidence of right ventricular hypertrophy or possibly dilation. The mechanism of this type of change is unknown, but rotational events and possibly areas of electrical silence may be the cause. At autopsy this patient had marked right ventricular hypertrophy, an essentially normal left ventricle, and no myocardial infarction.

A and *B* of Fig. 6 should be compared. In *B* there is similarity to the "axis illusion" phenomenon with a false infarct. Careful inspection shows, however, that the P axis is different and that the P is not flat in Lead I nor inverted in Lead aV_L. Furthermore, the S-T and T changes are as one would expect with an anteroseptal infarction, which was present at autopsy.

Another pattern frequently encountered in emphysema is of interest. Recently the electrocardiographic manifestations of hypertrophy of the crista supraventricularis have been investigated.[8] As in atrial septal defects this is evident by a terminal vector directed to the right. But in emphysema this tends to be directed to the right, upward, and usually somewhat posteriorly. Thus, the pattern of crista hypertrophy in the presence of emphysema is manifested by a wide S wave in Leads I, II, III, V_4, and V_6. Fig. 3 demonstrates the development of this pattern, and this should then be taken as evidence of an abnormal right ventricle (cor pulmonale) when it is clearly evident. The bottom tracing in Fig. 3 was recorded approximately 4 years after the top tracing. The development of wide S waves in Leads I, II, III, V_4, and V_6 is clear. At autopsy this patient showed marked hypertrophy of the crista supraventricularis in addition to pulmonary emphysema.

Special procedures. Pulmonary function studies are of obvious importance in evaluating the patient with emphysema and his response to treatment. Except for inference, however, they tell little more about the state of the right ventricle than can be gained by other means. Cardiac catheterization, angiocardiography, and related diagnostic procedures are seldom employed in the routine clinical evaluation of a patient with emphysema and suspected cor pulmonale. The detection of enlarged pulmonary vessels and especially the quantitation of pulmonary vascular pressure are of obvious importance, but again, except for inference, these do not indicate directly whether the right ventricle is abnormal. These are important procedures from the research standpoint, but at present they are seldom used in routine clinical management of a patient with emphysema and cor pulmonale.

Conclusions

Problem areas arising in the clinical diagnosis of cor pulmonale due to emphysema have been briefly covered in this discussion. The unique effect that emphysema exerts in masking the diagnostic features of cor pulmonale has been noted. That this masking effect includes not only the history and physical findings but also laboratory data, radiography, and electrocardiography has been stressed.

At times the clinical diagnosis of cor pulmonale may be extremely difficult to make. It is noteworthy, however, that the clinician has little more difficulty in borderline cases than does the pathologist, who even at the autopsy table frequently has difficulty in deciding whether a right ventricle is normal.

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Pargyline hydrochloride as an antihypertensive agent

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Sufficient data are now available to indicate that pargyline hydrochloride has antihypertensive properties which makes it unique in the class of drugs known as monoamine oxidase inhibitors. The manner in which it produces hypotension is unknown and is probably not related to its chemical action. In contrast to other substances which reduce blood pressure it has no ganglionic or peripheral nerve blocking action. There is little, if any, reduction of the blood pressure with the patient supine, but with the patient erect effective doses produce a prominent orthostatic effect. For this reason, this drug is recommended primarily for the treatment of hypertension of moderate to severe degree. As an effective antihypertensive it seems to be uniquely of value in the patient with a prominent elevation of blood pressure in whom the better known drugs either are ineffective or produce a marked depression. Reserpine or one of its analogues, which are known depressants, might even be continued with the addition of pargyline to reinforce their antihypertensive action and to counteract the depression. The average initial dose is 25.0 mg. daily, with a gradual increase each week of 12.5 to 25 mg. daily. The majority of patients when standing will show a significant fall in blood pressure at dosage levels of from 37.5 to 100 mg. daily. Our own experience parallels that of others. Almost all of 36 patients who were treated and followed for several months to one year demonstrated a significant orthostatic reduction in blood pressure. Tolerance to the antihypertensive action of the drug may occur despite repeated increases in dosage to as much as three times the presently recommended dose.

Today, the value of a drug is apt to be judged more by its side effects than its effectiveness as a therapeutic agent. Pargyline hydrochloride is no exception, hence the emphasis in the literature on the side reactions, which are minor compared with those of other commonly used antihypertensive agents. Nervousness and sleeplessness are commonly noted and may necessitate a reduction in dosage. Muscular twitching may also occur. Gastrointestinal and genitourinary symptoms are rare at the usual dose levels. Dependent edema with a gain in weight is occasionally noted. In such instances, the use of a thiazide diuretic as additional medication would be desirable. Although transient derangement in liver function is reported in the literature, we have not encountered this to date.

The future status of pargyline hydrochloride is still uncertain. As with all new drugs, particularly enzyme inhibitors, caution is required in its use. Appropriate laboratory studies to rule out any adverse

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effect on liver function and bone marrow should be made from time to time

Generic name: Pargyline hydrochloride. Trade name: Eutonyl.

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Dietary carbohydrate and ischemic heart disease

In the wealthier countries, the prevalence of ischemic heart disease (I.H.D.) has risen fast and to an alarmingly high level. It is right then that we should look at the environmental changes which have occurred in these countries and which are not yet evident in the poorer countries, to see whether they provide clues as to the possible causes of the disease. The magnitude of the increase in prevalence suggests that we should look for considerable changes in environment. In this connection, we may reasonably suggest that one of the many reasons for doubting the importance of the role of dietary fat in causing I.H.D. is that the magnitude of change in the amount and composition of the fats we eat has not been very large. Indeed it has been small enough still to be the subject of argument.

The major environmental changes which have affected man's person are the increase in the smoking of cigarettes and the decrease in physical activity. Between 1920 and 1960 the number of cigarettes smoked by the average Englishman increased from 1,100 to 2,800, and by the average American from 600 to 3,800. In the same period the number of motor vehicles in Britain increased from 360,000 to 7.5 million, and in the United States, from 9 million to 73 million. Other indices of increased sedentariness could be quoted in terms both of leisure activities, such as radio and television, and of work activities in the factory and in the home. We are now too lazy to exert ourselves to the extent of brushing our own teeth.

A third major change is in the food we eat, for we are now in the middle of man's second dietary revolution. In order properly to understand this, we must go back 8,000 years or so, before the beginning of civilization. At that time, man, like all other species of animals, got his food from hunting and foraging. He ate mostly meat and offal from the animals he killed and found as carrion; he ate relatively little in the way of vegetable foods—roots, leaves, fruits, and berries. Thus, his diet was relatively high in protein, moderately high in fat, and low in carbohydrate. When he began—uniquely in the animal kingdom—deliberately to produce food, he grew chiefly cereals and later other starch-rich foods. He began also to domesticate animals, both for work and for food. But in almost every part of the world into which he spread, he found it much easier and more productive to grow starch-rich foods rather than protein-rich foods. As a result his diet changed, so that he now ate far more carbohydrate, less protein, and no less fat. Economic circumstances, determined chiefly by the inevitable pressure of population against food supplies, have made it impossible until very recently for man to change his diet back toward the protein-rich, starch-poor diet of his early ancestors.

The first dietary revolution, then, was the discovery of cereals—the basis of civilization. It meant that there was a tremendous increase in the quantity of his food supplies, but a change also in the quality of his diet. The second dietary revolution has taken place chiefly during the last 100 or 200 years, in the few wealthy countries which have undergone industrialization. The increasing affluence which was responsible for the developments of science and technology, and the ability to apply them, led to a vastly increased availability of food. This came about by improvements in agriculture, transport, and food preservation. These, and the control of population growth by voluntary limitation of the size of the family, led to the present situation. Today, for the first time in the million or more years of man's existence, several hundred millions of individuals—although still only a small part of the total human family—can look forward to a lifetime of adequate food supplies. Until recently, recurrent hunger and famine was always part of man's existence. Today we can reasonably change the famous old slogan to "Millions now living will never die of hunger."

Within this framework of an increasing quantity of food, there has been a detectable change in quality. As though his natural food instincts direct man toward his primitive and largely carnivorous diet, increasing affluence has led to an increasing consumption of meat and other foods of animal origin. In terms of nutrients, there has been an increase in protein and fat, and a fall in starch. But a closer look reveals that the total carbohydrate in the diet has fallen very little, since the lower amount of starch is almost exactly matched by a higher consumption of sugar.

This has come about because the food processor has been responsible for two quite different processes. The first is the tremendously improved and extended methods of food preservation, so that we now have far better control of the ancient methods of salting, drying, and smoking, and also the new methods of canning, quick freezing, accelerated freeze drying, and, soon perhaps, irradiation. As a result, we in the wealthier countries can have an enormous range of foods wherever and whenever we wish. But, in addition, the food processor has more recently been able to separate nutritional also from palatability. Chiefly, he has been able to ...

late, purify, and produce very cheaply the essence of sweetness—sugar. In the days before civilization, man satisfied his taste for sweetness by eating fruit. Today he can have concentrated sweetness, with attractive flavors and colors, but quite free from the vitamins, the mineral elements, and the bulk of the fruit.

The rise in the consumption of sugar is far greater than the change in any of our other major foods or food constituents. In Britain, about 200 years ago, we ate 4 pounds of sugar a year; 100 years ago we ate about five times as much or nearly 25 pounds a year; today we eat something like 120 pounds a year. Similar changes have happened in other wealthy countries, and are beginning to happen in the developing countries. And since much of our sugar is taken in the form of candies, ice cream, biscuits, and cakes, we can attribute part of the present consumption of cereals, and some sort of fats, to the highly palatable foods which we eat because they are sweet.

We can say then that the ability to manufacture foods, from isolated and synthetic materials of high palatability has kept up our consumption of carbohydrate to levels higher than those we should have reached if we had access only to our ordinary ancient foods. Thus, the second dietary revolution brought about by science, technology and affluence has two components—an increased quantity of food to which the food processor contributes by methods of food preservation and a changed quality of food which he contributes by his ability to manufacture new foods, especially foods rich in sugar.

We began by saying that three of the considerable changes in man's environment which are related temporally—and perhaps causally—to the increased incidence of I.H.D. are cigarette smoking, diminished physical activity, and the recent dietary revolution. The last we can now identify more closely as the availability of an abundance of food for the whole life span of most of those who constitute the affluent societies, together with a persistence of a diet high in carbohydrate, especially sugar, in circumstances in which we might have expected a fall in carbohydrate. Moreover, the relevance to our discussion on I.H.D. is not only that these changes in dietary sugar are greater than, for example, the changes in dietary fats, but also that there is in fact now an increasing amount of evidence, both epidemiological and experimental, that carbohydrate in general, with sugar in particular, is the likely dietary component amongst the complex of etiological factors of I.H.D. Reviews of some of this evidence have been published by Cohen[1] and by Yudkin.[2]

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Stress and occlusive coronary artery disease

Whether or not stress in any form can be causative as a factor in the development of precocious coronary disease is still disputed. The idea was vigorously opposed by Sprague, who is supported in similar terms by Master[8] and Wright. Their main arguments, which influence a substantial body of opinion, rest on the impracticability of measuring *the impact of stress and also the contrast between* the protection afforded by modern civilization and the harsh environment of, say, Arnott's Chinese peasant. Emotional stresses too, Sprague observed, have always been with us and no doubt contributed in Thoreau's day to the quiet desperation of his American contemporaries. The opposing opinion has been put forward with growing emphasis by Russek and other writers with such differing viewpoints as Dock, Wolf, Reid,[20] and Morris,[11] who are now willing to accept a loosely defined stress as part of a multifactorial causative system.

At least some of the difference in opinion can be traced to the ambiguity of the word itself. "Stress" has a double derivation and contains two different, even antithetical meanings.[8] On the one hand it is a shortened form of "distress," which has descended through the old French *destrece* from the late Latin *districtus* and has come to mean hardship or affliction as of one who is pulled to pieces. The parallel derivation of the same word is from [illegible], a *halter*, through the Latin *stringere*, to draw tight, and still implies a constraining force such as the grip of emotion. Thus, in a medical context, whereas Selye equates the word generally with physical hardship, Osler in warning us against the dangerous stresses of modern life seemed rather to have in mind some form of emotional stringency. It is now being asked whether a causative link can be established between emotional stresses and coronary artery disease and also whether such stresses are tending to replace in importance the disappearing Selyean stresses of hardship as the general standard of living rises. An interest in this field is all the more welcome because most investigators

during the last decade have concentrated on the biochemical and dietetic aspect of the problem and therefore on general atherosclerosis rather than on selectiv coronary artery disease.

Precise information on the somatic effects of emotional stimulation is being accumulated by experimental work that owes much to the initiative of Friedman, Rosenman and their associates. In addition to the familiar pressor response emotional stress is now know to provoke an abrupt rise in the serum levels of nonesterified fatty acid and cholesterol, to increase the viscosity of the blood,[10] and to shorten its clotting time. Thus, with remarkable teleological thoroughness the body is provided with readily assimilable muscular fuel and is also prepared against possible wounds. These mechanisms appear to be organized in the hypothalamus.[14,15] Whether their repeated frustration is, in fact harmful can only be inferred, but the persistence of preparations for physical reaction of violence into an age in which social convention prevents such behavior reminds us that civilization with its special stresses is a biologic novelty to which we may not yet have adapted ourselves successfully. It remains a striking fact that each of the three mechanisms currently held to be involved in coronary atherogenesis—lipemia, intravascular thrombosis[16] and internal wear-and-tear[17-19]—are affected provocatively by emotional stimulation.

The alternative and complementary approach to the problem starts with a random group of patients known to have coronary artery disease and investigates the stress content of their lives up to the time of the illness.[20-26] Since such an enquiry enters the relatively imprecise field of sociology important experimental difficulties appear and less spectacular results can be expected. In the first place a clear definition of the type of emotional stress under examination is needed, so that observations can be repeated by other investigators in the same terms. Secondly since some form of questionnaire or interview is necessary a way must be found to eliminate bias on the part of both the subject and the observer. Thirdly comes the difficulty of finding a standard of comparison, the normal or non-case, which has proved to be elusive even in purely pathologic work.[27,28]

A recent pilot-scale investigation[29] was planned so as to avoid these sources of error by pairing the coronary subjects with fully matched controls chosen from patients attending the gastrointestinal unit of the same hospital. Since the organic digestive disorders are also linked with stress by the lay mind an identical approach could be made to propositi and controls by the nonmedical interviewer who remained unaware of the clinical group to which each subject belonged. No attempt was made to assess the character or temperament of those interviewed, but the aim was to examine, as objectively as possible, the environment in which they lived and worked. Stress was defined for the purpose of the enquiry as exposure to situations which stimulated anger or fear of sufficient intensity to be recognized as such at the time and recalled at later interview. The estimated frequency and severity of these emotional stresses was found to be greater in the coronary patient in 16 out of 24 matched pairs, with equal values in 4 pairs and with the control having more stress than the patient in the rest. On analysis the incidence during home life was roughly equal in the two groups; the main difference between them appeared in the field of work, travel and leisure activities. The stresses which occurred at work were noted to arise more from unsatisfactory personal relationships, e.g. between manager and subordinate or between colleagues than *from the* nature of the employment itself. Seldom of great severity these stresses were characteristically repetitive and unavoidable.

It can be argued that this kind of stressful situation, or at least the opportunity for it, becomes more common in a highly organized society both because of improvement in methods of communication and also because of the increasing complexity of the business and industrial world and the interdependence of those engaged in it.

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Problems in histology and pathology of the intrinsic nerves of the heart

Fundamental questions are still "open" about the morphology of the heart intrinsic innervation, the evidence and significance of which are often forgotten or underrated in discussions of cardiac physiology and pathology. The need for wider information and deeper interest in regard to the intrinsic nerves of the human heart could be stimulated by a critical reappraisal of a series of recent observations, compared to other significant data collected on the subject.

Thick and widespread networks of nerves have been lately illustrated, both in specific and general myocardium, which have very little to share with the delicate branching of unmyelinated or poorly myelinated fibers depicted by former researchers as intracardiac plexuses.[1-4] The possible endings of nerve fibrils into the myocardium, either afferent or efferent, occasionally seen encircling muscle cells in loose spirals, coils, or whorls, has been there replaced by the evidence of large, dark strands running alongside each myocardial fiber and frequently surrounding entire muscle bundles in a terminal-plexus fashion. The impression arises that, altogether, the heart should be regarded as an extraordinary neuromuscular organ.

A sharp contrast in the techniques employed accounts for such a difference in histologic features, which could seriously challenge the background of current concepts in cardiology. The classic silver impregnations for nerves have been substituted by one for reticulum,[3] coupled to hydrolysis and digestion test; thereby the details of the single autonomic nerve fibers, their caliber and shape, are completely lost, as some collagenous binder ought to be responsible for their black impregnation. Thus, the results are so far from being comparable to those of traditional histology that a more complete discussion should be open about the validity of the technique in revealing nerve instead of collagen, reticular, or elastic fibers.

Moreover, electron microscopy has led to a better understanding of debated questions concerning the autonomic nervous periphery in the heart, namely, the ultimate branching of the plexuses and their relationships with myocardium.[5] It has been observed that nerve fibers lie close to specific and common myocardial cells, but neither as many nor as thick as revealed by the method for reticulum. These fibrils contain a few protoaxons inside the lemnoblastic sheet, but no collagen or precollagen binding substance seems to be strictly associated to them. Evidence of possible synaptic contact between micronerves and sarcolemma has been underlined, without constant evidence of a proper perimysial plexus.

Little attention has been dedicated to the pathology of the intrinsic nervous system, in comparison to other tissue components of the heart, and to the

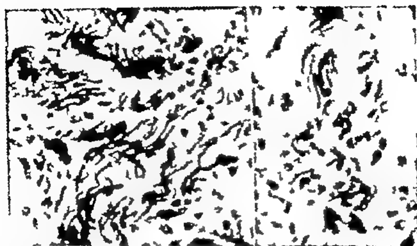


Fig. 1. Axons of intrinsic atrial nerves, showing diffuse granular degeneration (*left*) up to lysis and multiple interruptions (*right*) when infiltrated by granulocytes in recent myocardial infarction. (Bielschowsky-Gros ×630.)

emphasis upon neurovegetative derangements as cause of cardiac troubles. It must be maintained first, that the classic silver impregnations are necessary for studying nerve pathology by optical means. A method is unsuitable for this purpose if it fails to demonstrate the details of axon degenerative or abnormal regenerative changes.

With orthodox techniques a marked damage to nerve fibers and ganglia has been detected in coronarosclerosis, in various cardiopathies, and in the senile heart. Changes in the plexuses inside and around the pacemaker have been recorded in cases of atrial fibrillation, nodal rhythms, and supraventricular paroxysmal tachycardia, whereas the specific myocardium exhibited less significant alterations.[illegible]

With regard to myocardial infarction, the fate of the nerve network in the necrotic area has been overlooked, with a few exceptions.[illegible] Recently it has been pointed out that the involvement of nerves during the phases of ischemia and necrosis does not seem to be strictly parallel to the entity of myocardial damage as the axons undergo the most severe changes, from granular degeneration up to destruction (Fig. 1), in the further stage of leukocytic invasion.

The different metabolic requirements and sources account, likely, for such a discrepancy between nervous and myocardial lesions from lack of local blood supply but it looks to stand against morphologic and biologic evidence admitting that a delicate nerve network could largely survive the lytic activity of the granulocytes, whereas they infiltrate the infarcted zone.[illegible] The scars from healed infarct are, thus, devoid of nerve plexuses, although a few and probably interrupted fibrils, could be present at the periphery of hyaline patches. In milder myocardial fibrosis from a long-acting dystrophy however portions of the plexuses could actually survive, as observed in sclerosis of the sinoatrial node.[illegible] No significant participation of nerve structures in the sclerotic replacement of myocardium has been confirmed.

A firm believer in the necessity and value of furthering researches and collecting data on the whole subject, I would like to recommend nevertheless, extreme care in choosing techniques and drawing sentences, since unsound arguments might become deeper sources of confusion than unsolved questions.

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Series vascular resistances

I the assessment of the f nctional implications of pathologic arterial occlusions, one is often struck by how much the arterial lumen can be diminished with minimal embarrassment t the peripheral circulation. Arteriographic studies frequently show profound decreases i the caliber of major arteries w th only m nimal evidence of ischemia of the tissues which they supply I fact, it has been shown that the diameter of the carotid artery in situ must be decreased t *10 per cent* of its normal alue before flow falls t one half

I an earlier paper[2] we called attention to the idely known fact that although a partially oc cluded artery could supply the resting, or minimal, requirements of group of tissues, vasodilatation in one scula bed supplied by this artery could divert the limited supply of blood nd produce a relativ ischemia of the parallel undilated beds A gmented flow through the dilated bed diminishes the pressure i the segment of artery distal to the occlusion, thus depressing the gradient of pressure a ailable for the parallel undilated resistances to dimi ish flow The conditions which must be satisfied in order t produce di ersion of this sort ca be better ppreciated i terms of the relative magnitude of the hemodynamic resistances of the occl sion and of the several scular beds invol ed

Normally the pre-arteriola resistance in the extremities of ma is so small that, with ery few exceptions, the circulation i capable of meeting all of the demand of all ti sues in the area. I extraordinary situations, however it possible t demonstrat an inadequacy i the local supply of blood in normal individual during the initial phase of reactiv hyperemia of the forearm there i a profound drop i the directly measured brachial ar terial pressure Because the caliber of the arterioles is highly ariable nd is regulat d t sure adequat perfusion f the tissues, with reactive hyperemia the induced rteriola d latation is so great that the flow int the brachial artery (determined by the central arterial pressure nd the arterial resistance) cannot maintain adequat pressure t thi poi t. The widespread, profound arteriolar relaxation lowers the total *postarterial resistance* in that ex tremity to such a level that the *rterial resistance* becomes significant fraction of the whole. With a normal aortic mea pressure of 100 mm Hg the usual pre-arteriolar pressure is 85 capillary pressure bout 25 and enous pressure about 5 mm. Hg thus, only 15 per cent of the t tal resistance is in the arteries. During local maximum arteriolar dilatation, the ortic pressure might remain 100 but in the local artery the pressure drops to about 40 mm. Hg Here, approximately 60 per cent of the total resistance precedes the arterioles. I his recent excellent book, Shepherd brings together much of the experimental evidence bearing on this point.

An increase i va lable perfusion pressure usually evokes an increase in the resistance which tends to maintai blood flow t normal level. Conversely drop in pre-arteriolar pressure lead to dilatation of the resistance vessels t restore flow The systolic pressure distal to major arterial occlusion in peripheral vascular disease was found to be significa tly diminished even in resting leg with pparently normal blood flow The pathologic increase in the pre-arteriolar resistance lowers the pressure i the distal part of the artery but, in resting tissue, ischemia is oided by a compensatory decrease in the local arteriolar resistance Under these circumstances the ratio of resistances assumed for the normal vascular bed is no longer tenable here the pre-arteriolar resistance has in creased, the postarteriolar resistance has decreased, and the capacity of the local asomotor system to compensat for further arterial pressure drops the reserv is inadequat Now normal physiologic vasodilatation i cognat beds may decrease the available local arterial pressure and thus induce ischemia in the parallel, odilated tissues.

The wide range of pre-arteriolar resistances which can be toler ted by the tissues in their rest ng condition i significa tly dimi ished by the larger blood flow demands which are met with i the circumstances of muscle dilatation during exercise or skin dilatation as i heat regulation.

I the case of the carotid artery cited bove the

circulatory demands of the cerebral tissues undergo relatively small changes so that significant occlusion of the artery is tolerable.

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Letter to the Editor

Evaluation of anticoagulant therapy for myocardial infarction

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To the Editor

The use of anticoagulant therapy for the treatment of myocardial infarction continues to be widespread despite some recent expressions of doubt in regard to the merits of this approach. In the May 1963 issue of the *American Heart Journal* an annotation on this subject by A. L. Jacobs appeared which raised certain questions in regard to the validity of the conclusions of the report of the Committee on Anticoagulants of the American Heart Association. Since some of the statements made by Dr Jacobs are based on deductions that do not stand up under more complete analysis, it seemed necessary that this supplementary annotation be published. These points of issue will, therefore be considered serially.

Whereas it is true that, although sought for ideal randomization was not achieved in this series, this has been true in varying degrees in all large series on anticoagulant therapy thus far published, including that of Hilden et al. The fundamental question is whether the deviations from randomization produced significant differences in factors other than anticoagulant which affected the ultimate results. In other words did these deviations produce the favorable results attributed by the report to anticoagulant therapy? This question was most carefully reviewed with the aid of exhaustive analyses and extensive significance testing and the discussion was covered in detail in the original report for those who wish to consult it. See particularly summaries on pages 56-59, 172 174, 191 192, 252 253 and 345-347. The conclusion was that there was no significant net effect in favor of anticoagulants. A major bit of evidence in this regard was the fact that the percentage of cases which were severe at onset was 31 per cent in the treated group as compared with 26 per cent in the control group. Other points of issue will be considered below.

Dr Jacobs statement in regard to secondary myocardial infarctions includes the phrase that we "presumed *them all to be potentially preventable* by anticoagulant therapy." This is a gross misrepresentation of the content of the report. On page 407 we reported on the basis of autopsy evidence that a maximum of 71 per cent might have been avoided by "anticoagulant therapy of optimal level and duration." The same page includes the further comment, emphasized by italics, that "if these ratios are typical, it is unrealistic to expect that all secondary infarctions or extensions in the myocardium can be prevented by anticoagulant therapy even under optimum conditions." Dr Jacobs also fails to mention the statistically highly significant differences in the number of clinically diagnosed intracardiac complications in the total control and treated groups, namely in 15.8 per 100 cases in the control group and in 5.1 per 100 cases in the treated group (page 214). Furthermore the incidence of such clinically diagnosed complications as well as extracardiac thromboembolic complications was found on autopsy to have been consistently underdiagnosed about one in three of the former and seven in eight of the latter were missed clinically (page 418). These differences certainly appeared to have some relationship to the effect of anticoagulants on thromboembolic processes, and this point has been repeatedly confirmed by many others.

We are in agreement with Dr Jacobs that the conclusions of studies if based on death rates alone may be subject to confusion due to other factors. The report contained detailed consideration of this problem (see Figure 127, page 308). Many subgroups were considered based on prognostic indicators. Our figures showed that there was a net saving for all subgroups analyzed whenever the over-all percentage of those dying was 2 per cent or more (see Figure 143, page 346). Division into subgroups inevitably results in some of them becoming too small to be statistically significant, a problem which is even more evident when the total number of cases studied is small. This was a major reason for the decision to continue the original series to the large number of 1,031 cases.

We have previously discussed the fact that the primary significance of the difficulties in randomization inherent in all such series published to date is their potential for producing extraneous deviations in the outcome under consideration. After exhaustive study the group in the American Heart Association study was demonstrated not only to be essentially comparable in spite of sampling deviations, but also to show such a consistent picture of benefit associated with anticoagulant regardless of the characteristics of the patients, that practically any type of sampling bias that might conceivably have occurred, if statistically corrected for could not have negated the broader outlines of the report's conclusions. Evidence on these points was developed in many places throughout the report and anyone who takes the time to read it in detail can

*With special reference to the annotation by Dr A. L. Jacobs in the May 1963 issue of the *American Heart Journal*, Volume 65, page 716.

find. Although Dr Jacobs was correct in stating that in the first week of illness more patients developed signs of heart failure in the control than in the treated group, he failed to note that the differences were not statistically significant for any of the five indices of heart failure on which data were collected (page 173). He made no reference to the many indices on which the treated group reflected a less favorable, rather than a more favorable prognosis than did the control group figures. As mentioned above, among these one of the most important was the percentage of cases judged to be severe at onset (control group 26 per cent, treated group 31 per cent). This difference was consistent with the slightly higher percentages for the treated than for the control group on initial shock, maximum pulse of 90 or more, drop in blood pressure, elevated sedimentation rate and friction rub.

There have been a very large number of confirmatory reports in the intervening years. The literature contains approximately ten confirmatory reports for each negative report; the total now reaches more than 100 from many countries. Although the weakness in many of these reports is evident and has been commented upon, this is no less true of the negative reports. Dr Jacobs failed to give a proper impression of the total weight of evidence when he selected three affirmative and three negative papers as if they represented the balance upon which judgment should be made at this time, especially when the studies he selected were not comparable as to protocol.

Dr Jacobs commented on lack of standardization of conditions of hospital care. We have previously emphasized this problem in clinical research. It exists between different hospitals but also between wards or services within each hospital. In all studies efforts must be made to minimize it, and more important, analyses should be carried out to determine whether it is affecting the results. Chapter II of the report explains the great efforts which were made in this regard, first during a trial run period (the results of which were discarded) and then throughout the study. Among others, these included the use of detailed instructions and forms for reporting, repeated meetings of members of the Committee, on-site visits by the central laboratory staff especially by Dr Charles Biple who devoted full time to this project, rechecks of prothrombin techniques for comparable results, circulating news-letters and numerous other techniques to insure the best possible standardization. In Chapter VII, devoted to the analyses of all available data on the management of the illness, the conclusion was reached (page 191) that "no evidence of lack of comparability in treatment in respects other than anticoagulant therapy was found that was not readily explainable either on a chance basis or in terms of an indirect relation to anticoagulant therapy with one exception, namely a difference of borderline significance for private duty nursing. The effect of this difference on the outcomes under study was estimated to be minor or inconsequential" (pages 184-191).

Dr Jacobs was correct in stating that the patients included both ward and private cases unequally distributed among the sixteen hospitals. Some hospitals contributed only private or semiprivate cases, some only ward cases, and some both types. However, for a study of the effect of the drug what is primarily important is not the type of care in and of itself but rather whether the care received, whatever it was, impinged in approximately equal degree on both the control and treated groups. Evidence of two types on this point is contained in the report. One indicates whether there was any over-all difference between the control and treated groups in the percentage of ward cases. It was found (page 182) that the percentage of ward cases in the control group was 64.7 per cent and in the treated group 59.1 per cent. This difference when tested was found to be not statistically significant. The second indicates whether hospital by hospital, the percentage of ward cases in the control group was approximately similar to the corresponding proportion in the treated group. On this point, the last column in Appendix Table 33 indicates that eight or half of the sixteen participating hospitals contributed identical percentages of ward cases to the control and treated groups. For two others the percentage of ward cases in the two groups differed by only one percentile point. For two additional hospitals (one involving a partial estimate) the difference indicated was only two percentile points. One additional hospital (reporting a total of only 47 cases) differed by eight percentile points, not a statistically significant difference in this instance. Only three of the participating hospitals differed by more than this amount. In other words, only three or at most four hospitals out of sixteen could be considered to have differed enough in the proportion of ward cases in the two groups to have conceivably had a significant effect on outcomes. As will be shown below, omission of these four hospitals from computations of the percentage dying in the control and treated groups has only a very minimal effect on the decrease in deaths associated with the use of anticoagulant therapy.

The report points out that the fatality rate for ward cases was substantially higher than for private and semiprivate cases and this seems to have been the consistent experience in other reported series. However, Dr Jacobs' explanation in terms of a higher proportion of mild cases in the admission to private and semiprivate groups clearly does not fit the facts as obtained in this study. The percentage of cases of severe illness at onset was the same for both private and semiprivate and ward cases (within one percentile point—see footnote on page 324). Additional computations based on Appendix Table 34 further confirm this conclusion. It is clear therefore that the lower death rates in the private and semiprivate cases cannot be explained in terms of mildness of the attack at onset. The fact that, according to our protocol, cases of doubtful diagnosis as well as those in which death occurred within the first 24 hours were eliminated from the study may have eliminated the type of difference noted elsewhere. These two factors applied equally to both treated and control series. Although the figures indicated that the services of a private duty nurse were more frequently utilized by the private and semiprivate patients and might be assumed to account for some of the difference we noted (page

hat perhaps ard cases also tended to be n general ondition ph ically relation to t n nd othe factors which would not be re l t m of seriousness of the ttack, tha pri t patients t the time of admission \ i l ual report and personal observations made g he ing ar ha tended to confirm p n bu ore detailed tudies on this poi t uld be desir ble.

D Jacobs ndertook t explore this matter of gher death rates in the ward cases by dividing the mple subgroups of (1) hospitals contributing l ard ases 2 hospit l contributing pri ate semipri te cases lmost exclusi ely (3) hos- int buti ng bo h types This technique uces he siz of the samples and hence makes the more l iect t chance fluctuations and con- ue tl l ble w h the result that the mean- l h larg and mall differences are unclear l u rs eport we lso explored differences hospit l t he pital n iderable detail but the tabili of small samples rendered sou d deduc tions mpossible I included (page 309) that pooling of the data improved markedly the com- parabil t of the con rol d treated groups.

F rther are be wer t the question Dr Jac b ppe red l k g can be found as follows ed the qu n nd ns ered t (page 325 C uld he fa l general surv al record of the tre t d gr up l d reported as seemingly due to u l h p be due rather t the some h proportion of ward cases the con- l u Thi question ca be nswered by m l ng the de th rates reported in this section l d t ndardized for age in uch w that the pr port n of w d and priv te cases is the same in he ontrol nd treated groups as in the total sample. When th is done the percentage dying in the con l group becomes 2 5 per cent nstead of 23 4 per en nd the treated group 16.4 per cent n- t ad f 16.0 per cent. The further correction obt ned has onl minor consequences. A very *stan ial d fferenc fatality ates by treatment groups rema ns that ot be explai ed term of the proport on of ward ases the control group*

W have also made a till more rigorous test of our data since being challenged by D Jacobs on this poi t. Through the use of Append Tables 33 nd 37 it is possible to compute the percentage of cases dying i the t o groups, om tting all the four pr viously mentioned hospitals hich reported deviations of more tha two percentile poi ts in the proportion of ward cases i their control as com- pared with their treated groups. The results for the other twelve hospitals compared with the total sample are shown n Table I (*below*)

From these findings, it is evident that hatever imbalance may have occurred i the proportion of ward cases in the two treatment groups in a few hospitals could not have been the cause of the dif ference in the survival rates, Dr Jacobs com- ments would lead the reader to believe. Moreover since findings on thromboembolic complications showed only very minimum nd insignificant dif ferences between ward and private or semiprivate care (pages 238-240) the over-all findings of the study in this respect also cannot be attributed to any imbalance between treatment groups i regard to ard care.

Contrary to Dr Jacobs suggestion, at no time have we recommended the *routine use* of anti- coagulant for myocardial infarction or for any other purpose, but have strongly recommended that they be used only with discrimination. There are ma y contraindications for their use which in- clude numerous conditions involving patients, and which have been repeatedly listed by us and by others. I addition, other factors must be considered, and these nclude the qualifications of the physicia and his laboratory geographic location of the pa tient, and many others. It is true that some physi cians believe that they can determine on the first day after a myocardial infarction whether a in- dividual patient ill develop thromboembolic complications later and they decide on that basis whether anticoagulants should be started then. Unfortunately our data were not reassuring in regard t the accuracy of prediction, even though examined diagnostic subgroups very carefully. In fact, when the umber of thromboembolic com-

Table I

	Number of cases		*Percentage dyi g*		
	Control	*Treated*	*Control*		*Treated*
			As r ported	*Corrected for exemption i treatment**	
12 hospitals i which per cent of ard cases i control and treated groups as closely comparable	305 (66 death)	405 (60 deaths)	21 6%	23 6%	16 3%
Total sample 16 hospitals	442	589	21 7%	23 4%	16 0%

*These percentages include estimates for deaths calculated to have been prevented by giving anticoagulants to 33 patient i the ont ol group after thromboembolic com ication had developed—a procedure permitted by the original research design.

plications was analyzed in terms of number per 100 cases, there was no subgroup, regardless of good prognostic indications, which fell below 28 thromboembolic complications per 100 cases when anticoagulants were withheld. Anticoagulant treatment was associated with substantial reductions for all groups (page 253 Figure 107) regardless of type, and appeared remarkably similar for all subgroups analyzed. When one considers deaths instead of complications, the drop in deaths associated with anticoagulant therapy is found to have been particularly conspicuous among those cases in which the illness was diagnosed as mild or moderate at onset (pages 330 346) In our study there was floor below which thromboembolism did not seem to fall, regardless of the type of case.

Of equal importance was the finding that the risk of hemorrhage seemed to be positively correlated with the risk of thromboembolism. The findings (pages 276-280) indicated that good-risk cases showed definitely lower hemorrhagic risk than did poor-risk cases In fact, only one instance of severe bleeding diagnosed clinically occurred in good-risk case (Table 115 and Fig 119) Moreover not single instance of good-risk patient whose attack was also mild at onset was found in the entire series in which hemorrhage was either the immediate or contributing cause of death (pages 277 296, 441 442) Clearly the risk of fatal hemorrhage in cases with otherwise low risk of dying is way below the over-all rate from our study This should reduce the fears expressed by Dr Jacobs and others on the risk of well-controlled anticoagulant therapy to those who are not then in the serious and complicated state, and in whom the objective is the prevention of further thromboembolism.

The question of risk was further clarified by recent review of 250 consecutive cases of acute myocardial infarction treated at The New York Hospital where physicians are generally familiar with the technique of anticoagulant therapy These patients were treated by many different physicians rather than by one team. The purpose was to evaluate the total care of myocardial infarction and its complications as it was actually applied. There was therefore, no randomization Although details of this review will appear elsewhere certain of the findings were nevertheless revealing in respect to this discussion. These were briefly as follows Of the 250 cases, 169 (68 per cent) were male and 81 32 per cent) female 49 per cent were private and 51 per cent were ward cases 80 per cent were suffering a first infarct, 16 per cent second, 3 per cent third, 2 per cent fourth 179 received anticoagulants, 71 did not for the usual reasons including bleeding tendencies, immediate postoperative state and death before the first dose could be administered. The total death rate including both groups, was 19.6 per cent 6.8 per cent died in the first 24 hours, and 12.8 per cent died thereafter The total death rate was 14.5 per cent for males and 29 6 per cent for females

Of those receiving anticoagulant therapy (which consisted of heparin plus an oral anticoagulant or the oral anticoagulant alone) total of 9 5 per cent died For those surviving 24 hours, the death rate in this group was 6 7 per cent, No comparison can rightly be made with those not receiving anticoagulants, since the contraindications were in themselves serious In addition to the withholding of the anticoagulants. Nevertheless for the record, the total death rate in this group was 45 per cent. After the first 24 hours 25.3 per cent died. The most pertinent finding which relates to the question of risk was clearly found in the data on hemorrhage Taking as an index of significant bleeding (which is after all what we are concerned about) any degree which necessitates change in treatment including omitting even a single dose of anticoagulant or the administration of Vitamin K bleeding of this degree was encountered in seven of the 179 cases treated with anticoagulants (2 7 per cent) and there were no deaths from hemorrhage in this series Cardiac rupture with death occurred in five patients in four of these within the first 48 hours four occurred in females and four out of five had never received anticoagulants. These figures dealing with rupture are of interest mainly because they indicate that small numbers or subgroups in series such as this can fall one way or another in such to give impressions which may be incorrect but unfortunately are too often accepted as significant and included in misleading conclusions. Autopsies were performed in 60 per cent of those dying and confirmed the diagnoses.

These figures do confirm our repeated statement that if the technique is sound, even though it involves numerous physicians, the risk from hemorrhage today should be so low as to play little or no role in the death rate The solution to this problem is better training of the physicians, young and old, who undertake this therapy rather than concluding that the technique is too dangerous because it may be poorly used, and the experience at The New York Hospital and many other institutions has fully justified this position.

The question of ethics in the use of any form of treatment is one which every physician faces daily Most effective forms of treatment entail some risk and this is especially true for the techniques of our surgical confreres. In each instance, the physician must weigh the risk of the treatment against the risk of the disease in the absence of the treatment under consideration. Anticoagulation in skilled hands under suitable conditions carries, as in surgery much lower risk than in the absence of these positive qualifications. The new generation of physicians is increasingly well equipped to handle these drugs, and is more informed in regard to indications for using them. Use of these drugs must remain a matter for discrimination.

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CIRCULATORY PHYSIOLOGY: CARDIAC OUTPUT AND ITS REGULATION. By Arthur C. Guyton, M.D. Philadelphia, 1963, W. B. Saunders Company. 468 pages. Price $15.

This book is subdivided int 5 sections. The first of these contains a good general discussion of historic literature and methods for determining cardiac output, including their advantages and disadvantages. No ttempt is made to survey the literature exhaustively and each reader will, no doubt, find some of his f vorite references omitted but will also be rewarded by the discovery of others which he did not know. The second section concerns the regulation of cardiac pumping action, described mainly by modified Starling curves. The third section on regulation of venous eturn emphasizes its importance to cardiac output, and highlights particularly the concept of mea circulatory pressur and its subdivisions. This section is probably the most valuable part of the book, in that this particular phase of circulatory regulation has, in general, been discussed less extensively. The fourth section, concerning graphic and algebraic analyses of cardiac output egulation and the fifth section, concerning regulation of cardiac output in specific physiologic and pathologic states, present the author' analysis of the circulation in either graphic or mathematical terms.

This reviewer has great difficulty in deciding for whom the book is written. The medical student, with his crowded curriculum will scarcely find time which he can justifiably devote to such an esoteric analysis of the circulatory system. The general practicing physician would not be expected to be interested in this book, nor will those practicing a specialty outside of internal medicine. The internist practicing chiefly outside the field of cardiology will find the same material covered much more succinctly in standard physiology texts. The cardiologist may have considerable interest in the text but will be disappointed by the fact that he is already familiar th the parts that he can apply and that which he does not know has frequently been derived from experimental situations which are quite remote from the usual clinical status and may well not be applicable. The physiologist will undoubtedly be distressed by the fact that the book is epetitious the same variety of diagram occurs many times in the text and yet without clarification as to how t was constructed. Most of the time the eader does not know whether a graph was fabricated because this is the way t should be or whether it as made from actual experiments—done how many times and under hat conditions. The diagrams re so obviously stylized, geometric and clear cut that they could be either simplifications of large amounts of data, at best, or extrapolations from meager data, at orst. In general, the physiologist should find the first three sections of considerable interest and should be able to use them as a good source for reference material. The last two sections lose a great deal of their effectiveness from the very obvious fact that the formulas and graphs predict information which is already known, and can be tested only in that they predict the information which wa used in their construction. The author's basic argument that this mathematical analysis is justified because one has to start somewhere may or may not find support in each reader own particular prejudices.

The author states frankly that his primary purpose in writing the monograph has been to present an analysis of cardiac-output regulation which he has developed over the past 10 years. There is no question that he has done this. H has included ith hi ow analysis a considerable amount of information derived from the va t world literature concerning this subject. But there is little doubt that the book is highly slanted toward the uthor own point of view. In order to decide whether one wants to devote time to this book, then, one needs only to decide for how long he is prepared to look at the problem of circulatory regulation through the eyes of a well read, mathematically oriented physiologist in the field of basic circulation who has a flair for making complicated things sound simple.

VASCULAR SURGERY. By John B. Kinmonth, M.B., M.S. (Lond) F.R.C.S. (Eng) Professor of Surgery University of London. Charles G. Rob, M.C., M.A., M.D. M.Chir (Cambr) F.R.C.S. (Eng) Professor and Chairman, Department of Surgery, University of Rochester and Fiorindo A. Simeone, A. B., Sc.M. M.D. Sc.D (Hon) Professor of Surgery Cleveland Metropolitan General Hospital. Baltimore 1963 Williams & Wilkins Company. 501 pages. Price $19.

This is most ewarding and unusual treatise on vascular surgery. The three authors eminent clinicians and experienced teachers, have written a series of chapter on the practical aspects of this field. The concept that all vessels outside the heart, including the coronary arteries, belong to the peripheral circulation is certainly to be pplauded. Unfortunately a discussion of much of the valiant effort, including that of Vineberg, to improve myocardial revascularization is omitted.

Inevitably there is some overlap and some difference of opinion in the various chapters, but this only enhances the value of this presentation. The reader can get a bidimensional, nay tridimensional view of a given subject, and this is the best educational device for giving a picture in depth. Let the mature reader choose what he prefers to adopt. The organization of the material, however is rather loose.

Obviously in a rapidly changing field certain diagnostic and therapeutic methods could not have been included. Thus, in the discussion of differential renal function tests, Howard' test is dealt with in much detail, but neither Stamey' method nor the rapid 1 to 5-minute pyelogram with concentr tion of dye ... the more

side are mentioned nor is the determination of vanillyl mandelic acid (V.M.A.) for the detection of pheochromocytoma described.

These are, however, inevitable difficulties with an early deadline of manuscripts. A more important objection is the denial, on the basis of negative animal experiments, of the value of early sympathectomy and rapid rewarming in the treatment of frostbite. Clinical experience is to the contrary.

In the foreword the authors express their hope that "a earlier and closer contact between British and American thinking would result from such an endeavor as this. The reviewer heartily agrees with this trend and the yearly exchange of residents and registrars between teaching hospitals on the two sides of the Atlantic has already borne fruit. To further advance this concept, it would help if the source of equipment listed in the footnotes not be limited to British sources, since this will frustrate the American reader.

Printing, spelling, and illustrations—with few exceptions—are excellent. David Sutton's chapter on arteriography is superb. All in all this is an intellectual treat for anyone closely or remotely involved in peripheral circulation. And who is not?

Atlas of Vascular Surgery. By Falls B. Hershey, M.D., F.A.C.S., Associate Professor of Clinical Surgery, Washington University, and Carl H. Calman, M.D., F.A.C.S., Assistant in Clinical Surgery, Washington University, St. Louis. St. Louis, 1963, The C. V. Mosby Company. 307 pages. Price $18.

This atlas is an excellent addition to the library of any department of surgery or to the library of any resident in surgery who contemplates performing vascular surgery. It is well organized, with the material being presented in a logical and easy-to-follow progression of steps in the various operative procedures. It is complete in that almost all vascular procedures, arterial as well as venous, are considered, most of them in more detail than heretofore presented in surgical atlas.

The book is divided into three sections. The first, an introduction to vascular surgery with general principles and a chapter on radiographic techniques, is extremely well done. The second portion deals with the actual surgical procedures: indications for the operations, a general review of the anatomy of the regions, preoperative preparations, a step-by-step outline of the procedure with special precautions concerning the difficulties which the surgeon may encounter and the postoperative care with mention of the common complications and how best to avoid them. An effort is made by the authors to present the manner in which they handle a particular vascular problem. Although this may vary among vascular surgeons throughout the world, the method presented is usually one of sound judgment and technique. Among the differences that might arise would be the indication for endarterectomy versus bypass grafting in occlusive disease, the use of longitudinal arteriotomies in aortico-iliac endarterectomies, and the use of anticoagulants in aortico-iliac endarterectomies. The third section of the book, on amputations, is the least comprehensive of the three. The authors do not seem to have the same depth of knowledge of the techniques and postoperative care of the patient who needs the amputation as that which they showed in the previous section on the treatment of his arterial disease. They fail also to recognize one of the most helpful allies which the surgeon has in this type of patient—the doctor of physical medicine.

This book is, however, extremely well organized and written, superbly illustrated, and is outstanding in its clarity and simplicity of description of the various operative procedures. Although of dubious permanent benefit to the vascular surgeon, this atlas will be of major importance in the training of the resident in surgery.

Clinical Metabolism of Body Water and Electrolytes. By John H. Bland, M.D., Associate Professor of Clinical Medicine and Director, Rheumatism Research Unit, University of Vermont College of Medicine. Philadelphia, 1963, W. B. Saunders Company. 623 pages. Price $16.50.

This volume contains within it a large collection of material by various authors relating to the general topic of body water and electrolytes, with the stated aim of bridging the gap between basic and clinical investigation and bedside medicine. Some of the sections relate specifically to problems in the management of patients, whereas others deal more or less exclusively with experimental work designed to provide a deeper insight into the physiology of the turnover of fluid and electrolytes. Unfortunately, the relevance, or even potential relevance, of some of the material to future medical usage is not made explicit. As in all compilations of multiple authorship, the quality of the sections varies considerably—at times, with some careless writing. For example, on page 160 it is asserted that the limits of salt tolerance for normal man range between 1 and 10 Gm. daily. This is followed by the statement that "ingestion of 25 to 30 Gm. of salt per day leads to an immediate increase in body weight of 10 to 15 lbs." When one checks the reference cited, the statement is found that most of the subjects maintained body weight during salt loading, but lost some weight after load reduction, from which it was inferred that mild retention of fluid may have occurred during salt loading. It seems almost commonplace clinical experience that normal man can tolerate a daily load of salt well in excess of 10 Gm. without significant retention. On pages 93 and 94 the discussion of the behavior of water and electrolytes across a charged membrane leaves much to be desired, since some of the notations used in equations are not defined, their derivations are not made clear, and references are not given. In spite of these shortcomings, this book does represent an extensive compilation of material, with a laudable although very difficult aim in mind.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Reserpine

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The rauwolfia alkaloids extracted from the snakeroot of the serpentine plant are now recognized as cardiac agents of considerable interest and therapeutic value. As with foxglove and cinchona, the rauwolfia alkaloids, which originated in India, had long been used empirically for a variety of ills. In the past decade, since gaining popularity in the Western world, a wealth of clinical and pharmacologic data has been accumulated. The most widely used alkaloid, reserpine, has been found to have a number of congeners with similar effects. Of these, syrosingopine, deserpidine, and rescinnamine have been most actively investigated. Definite clinical advantages, if any, over reserpine have not been demonstrated.

Pharmacologic effects

After the administration of reserpine the stores of serotonin in brain tissue, platelets, and the enterochromaffin cells of the intestines are depleted. Depletion of the levels of serotonin in brain tissue is an early effect which seems to correlate with the tranquillity induced by reserpine. Stores of catecholamine in heart muscle, brain tissue, adrenal tissue, and the arterial tissue are similarly depleted. The mechanisms of these effects and their relationship to the clinical usefulness of reserpine are obscure. However, it seems likely that the depletion of catecholamine in hypothalamic centers diminishes the control which these centers normally exert upon the sympathetic nervous system, allowing apparent increased parasympathetic influences. Thus fully reserpinized animals and animals with certain hypothalamic lesions may behave similarly.

Further sympatholytic effects of reserpine are probably secondary to a drug induced reduction of peripheral sympathetic mediators. Apparently, under ordinary circumstances, such extensive depletion of stored catecholamine and serotonin has no adverse effect on patients or experimental animals. The effects on an organism under stress may be a good deal more apparent.

It is of clinical as well as experimental importance to note that reserpine may abolish the pressor responses to such agents as ephedrine and tyramine. Infusion of norepinephrine will restore adrenergic responses.

These effects of reserpine are of particular interest when one compares the clinical response produced by reserpine with that of such recently introduced agents as alpha methyl-dopa and guanethidine. These agents also deplete the stores of catecholamine by different mechanisms and have different clinical effects.

Therapeutic value

When used in hypertensive patients, reserpine alone is of value primarily in treating mild labile elevations of blood

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